



Executive function in HIV-affected children and adolescents: a systematic review and meta-analyses

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1 **Executive function in HIV-affected children and adolescents: a systematic**
2 **review and meta-analyses**

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Abstract

This review aimed to determine: whether EF is affected in children and adolescents (2-24-years-old) with perinatal HIV infection, perinatal HIV exposure without infection, and behaviourally acquired HIV. A systematic review (PROSPERO number: *) was conducted using 11 electronic databases (01.01.1981-09.07.2019) and 8 conference websites. Primary quantitative studies with EF scores on cognitive tasks and/or behavioural report measures were included. Meta-analyses were performed by EF subtype and subpopulations compared. 1789 records were found. Sixty-one studies were included in the narrative synthesis; 32 (N = 7884 participants) were included in meta-analyses. There was a distinct pattern of reduced EF in those with perinatal HIV infection on antiretroviral therapy compared to controls: pooled effect sizes were largest for verbal and visuospatial working memory, with smaller effects on planning, inhibitory control and set-shifting. Data were limited for other HIV-affected subpopulations. Perinatal HIV infection is associated with reduced EF with varying effect sizes for the different EF subtypes.

Key words:

Perinatally acquired HIV, executive function, systematic review, HIV-associated neurocognitive disorder, paediatric HIV, neurodevelopment

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29 Introduction

30 Executive function (EF), mediated by prefrontal cortices (PFCs), is a set of cognitive control processes
31 which regulate cognition and behaviour. EF develops throughout adolescence (Blakemore & Choudhury,
32 2006). There are three core interrelated yet distinguishable EFs: inhibition, working memory, set-shifting
33 (Miyake et al., 2000). EF demands occur in ‘cool’, emotionally neutral contexts (lateral PFC-mediated) or
34 ‘hot’, emotionally salient contexts (orbitofrontal PFC-mediated) (Blakemore & Choudhury, 2006; Casey &
35 Caudle, 2013; Poon, 2017; Prencipe et al., 2011; Zelazo & Carlson, 2012). HIV may affect EFs
36 differentially (K. A. Walker & Brown, 2018) with earlier insults during “critical periods” of frontal lobe
37 development associated with poorer outcomes (Anderson et al., 2010; Jacobs, Harvey, & Anderson, 2007).

38 HIV-related EF deficits may be related to irreversible central nervous system (CNS) injury before ART
39 initiation; ongoing neuroinflammation or systemic inflammation (Eckard et al., 2017; Kapetanovic et al.,
40 2014); ongoing CNS viral replication (Chahroudi, Wagner, & Persaud, 2018)(Dahl et al., 2013; Sturdevant
41 et al., 2012); ART neurotoxic effects (Crowell, Malee, Yogev, & Muller, 2014).

42 EF is important because it has been associated with various functional outcomes (Best, Miller, & Naglieri,
43 2011)(Miller, Nevado-Montenegro, & Hinshaw, 2012; Moffitt et al., 2011)(Koike, Hardy, & Richards,
44 2015; Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013)(Moffitt et al., 2011). In HIV-endemic contexts, EF
45 deficits may increase the risk of HIV transmission (Rosenberg et al., 2018) and non-adherence (Williams,
46 Geffken, Silverstein, & Storch, 2007). EF deficits may be amenable to improvement through interventions
47 (Alvarez-Bueno et al., 2017; Bangirana et al., 2009; Bergman Nutley, Darki, & Klingberg, 2014; Cerrillo-
48 Urbina et al., 2015; Diamond, Barnett, Thomas, & Munro, 2007; Holmes, Gathercole, & Dunning, 2009;
49 Kamijo et al., 2011; Klingberg et al., 2005; Lakes & Hoyt, 2004; Moreno et al., 2011; Smalley et al., 2010;
50 Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009; Zelazo & Carlson, 2012).

51 This review aims to determine: how the various EF subtypes are affected in HIV-affected children and
52 adolescents (2-24-years-old) (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018); the factors associated
53 with EF (potential predictors, markers and outcomes); EF effects of interventions. Hypotheses include:

1. different EFs are negatively affected to various degrees by HIV infection and HIV exposure in children and adolescents,
2. perinatal HIV infection has larger negative effects on EF than perinatal HIV exposure or living in an HIV-affected household,
3. perinatal HIV infection has larger effects than behaviourally acquired HIV.

Methods

Selection criteria

Eligibility criteria are listed in Table I. Three subpopulations were included to give a population-level perspective. In studies of children <10-years-old, perinatal transmission was presumed. Studies including adolescents 18-24-years-old were included if the population fell primarily within this age range or presented age-disaggregated data.

Studies with HIV-affected controls (perinatally HIV-exposed uninfected (PHEU) or perinatally HIV-unexposed, uninfected (PHU) living in HIV-affected households), healthy PHU controls or population norms were included.

69 ***Search strategy***

70 * searched 13 databases and 8 conference websites (Table II) using three groups of search terms (Table I,
71 Appendix 1) and search limits (Table II) (see protocol: PROSPERO registration number
72 CRD42017067813).

73 (Insert Table I here)

74 (Insert Table II here)

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After de-duplication, abstracts and selected full texts were screened for inclusion by independent reviewers (* and either * or *) with disagreements settled by discussion. * performed reference harvesting.

Study appraisal

* and * conducted appraisals independently using the 27-item Downs and Black checklist with modified scoring (Downs & Black, 1998; Hooper, Jutai, Strong, & Russell-Minda, 2008). Relevant criteria, predetermined by study type, were used (Tables II and III, Appendix 1) and a proportion quality score generated (85-100% excellent, 65-84% good, 50-64% fair, < 50% poor) (Hooper et al., 2008). Discrepancies ≤ 2 points were resolved by averaging; > 2 points by joint re-scoring. Quality assessment affected meta-analytic weighting.

Data extraction

* extracted data (Table IV, Appendix 1) into tables. *, * and * checked for inaccuracies. Effect sizes (standardised mean differences with Hedge's correction) were calculated using MetaXL Version 5.3 (Hedges & Olkin, 1985).

Meta-analysis

Aggregate data meta-analysis occurred using unadjusted means and standard deviations. Where necessary, means were reflected for consistent directionality. If studies reported 95% confidence intervals, standard errors, or subgroup results, these were converted or combined (*Cochrane Handbook for Systematic Reviews of Interventions*, 2011) (Table V, Appendix 1). In longitudinal cohorts, baseline data were used. Separate meta-analyses were performed by EF type and subpopulations if at least two studies were found. EF types meta-analysed: verbal working memory; visuospatial working memory; inhibition; set-shifting; planning; global EF (caregiver-report); global EF (self-report). Subpopulation comparisons were:

- PHIV on antiretroviral therapy (ART) ($\geq 70\%$ sample on ART) versus healthy PHU controls;
- PHIV slow progressors not on ART (Lechenadec et al., 2007; Muenchhoff, Prendergast, & Goulder, 2014; Ofori-Mante et al., 2007) versus healthy PHU controls;
- PHIV on ART versus perinatally HIV exposed uninfected (PHEU);

- 101 • PHIV versus mixed PHEU/PHU;
- 102 • PHEU versus PHU;
- 103 • PHIV CDC C versus non-C;
- 104 • behaviourally acquired HIV (BHIV) versus HIV-negative controls.

105 We used quality effects models in MetaXL Version 5.3 (Doi, Barendregt, Khan, Thalib, & Williams,
 106 2015a, 2015b; Doi & Thalib, 2008). Between-study heterogeneity was assessed using Cochran's Q and
 107 I^2 , and publication bias using Doi plot asymmetry and LFK index (Furuya-Kanamori, Barendregt, &
 108 Doi, 2018). Effect size interpretation used Cohen's rule (small $d = 0.2-0.49$; medium $d = 0.5-0.79$; large
 109 $d \geq 0.8$) (J. Cohen, 1988).

110 *Qualitative synthesis*

111 Outcomes related to associated factors and intervention effects were described in the narrative synthesis.

112 **Results**

113 The search found 1784 non-duplicate records (1987-2019) and five more using reference harvesting (Figure
 114 1: PRISMA flow diagram). Abstract screening excluded 1363 records; 396 records underwent full text
 115 review (Figure 1). 61 studies (93 records) were included with 32 studies (34 records) meta-analysed
 116 (Cohen's kappa = 0.81). Eight studies required data pre-processing (five subgroup combination; two
 117 confidence interval conversion; one standard error conversion).

118 (Insert Figure 1 here)

119 Observational studies ($k = 52$) included: 20 longitudinal; 32 cross-sectional (Tables A and B, Appendix 2).

120 Intervention/experimental studies ($k = 9$) included: eight randomised controlled trials (RCTs); one pre-post
 121 study (Table C, Appendix 2). Data from 12373 participants were included ($n = 7884$ in meta-analyses):

- 122 • 5417 (44%) HIV-positive: 5083 (41%) perinatally acquired HIV (PHIV); 334 (3%) behaviourally
 123 acquired HIV (BHIV).

- 6874 (56%) HIV-negative: 2679 (22%) perinatally HIV-exposed uninfected (PHEU); 3254 (25%) perinatally HIV-exposed uninfected (PHU) not living in HIV-affected households; 1123 (9%) mixed PHEU/PHU living in HIV-affected households.

Population age composition: 66% children and adolescents; 20% adolescent-only; 15% child-only. 37 studies (61%) were conducted in low- and middle-income countries (LMICs) (44% Africa-based). The mean quality assessment score was 60% (range 11-92%).

Perinatally acquired HIV compared to healthy perinatally HIV-unexposed uninfected controls

Verbal working memory

Meta-analysis of fourteen studies comparing PHIV on ART to PHU (PHIV n = 1245; PHU n = 886) (Bisiacchi, Mento, Tarantino, & Burlina, 2018; M. J. Boivin et al., 2018; S. Cohen et al., 2015; De Pereira & Cunha, 2012; Debeaudrap et al., 2018; Haase, Nicolau, Viana, Barreto, & Pinto, 2014; Hoare et al., 2016; James & Ittyerah, 2016; Linn et al., 2015; Milligan & Cockcroft, 2017; Phillips et al., 2018; Puthanakit et al., 2013; Ravindran, Rani, & Priya, 2014; Willen, Cuadra, Arheart, Post, & Govind, 2017) found a large, significant effect with high heterogeneity (Figure 2A) and evidence of publication bias (LFK index = -2.19; major asymmetry).

Meta-analysis of three Africa-based studies comparing slow progressors not on ART to PHU (PHIV n = 133; PHU n = 155) (Bagenda et al., 2006; Hoare et al., 2012; Ruel et al., 2012) found a small, insignificant effect with low heterogeneity (Figure 3A) and evidence of publication bias (LFK index = 4.13; major asymmetry).

Visuospatial working memory

Meta-analysis of five studies comparing PHIV on ART to PHU (PHIV n = 670; PHU n = 479) (Bisiacchi et al., 2018; M. J. Boivin et al., 2018; Milligan & Cockcroft, 2017; Puthanakit et al., 2013; Willen et al., 2017) found a medium, significant effect with high heterogeneity (Figure 2B) and evidence of publication bias (LFK index = -1.39; minor asymmetry).

148 Inhibition

149 Meta-analysis of four studies comparing PHIV on ART to PHU (PHIV n = 401; PHU n = 327) (M. J. Boivin
150 et al., 2018; Haase et al., 2014; Hoare et al., 2016; Milligan, 2016) found a medium, insignificant effect with
151 high heterogeneity (Figure 2C) and evidence of publication bias (LFK index = -3.16; major asymmetry).
152 Meta-analysis of two studies comparing slow progressors not on ART to PHU (PHIV n = 105; PHU n =
153 118) (Hoare et al., 2012; Ruel et al., 2012) revealed no effect with low heterogeneity (Figure 3B).

154 Set-shifting

155 Meta-analysis of seven studies comparing PHIV on ART to PHU (PHIV n = 672; PHU n = 340) (Bisiacchi
156 et al., 2018; S. Cohen et al., 2015; Hoare et al., 2016; Phillips et al., 2018; Puthanakit et al., 2013; Ravindran
157 et al., 2014; Willen et al., 2017) found no effect with high heterogeneity (Figure 2D) and evidence of
158 publication bias (LFK index = -3.50; major asymmetry).

159 Planning

160 Meta-analysis of six studies comparing PHIV on ART to PHU (PHIV n = 409; PHU n = 376) (Bisiacchi et
161 al., 2018; M. J. Boivin et al., 2018; Debeaudrap et al., 2018; Haase et al., 2014; Linn et al., 2015; Yadav et
162 al., 2018) found a medium, significant effect of HIV with low heterogeneity (Figure 2E) and no evidence of
163 publication bias (LFK index = 0.04; no asymmetry).

164 Global executive function

165 Meta-analysis of two studies comparing caregiver-reported global EF problems in PHIV on ART to PHU
166 (PHIV n = 304; PHU n = 235) (M. J. Boivin et al., 2018; Ezeamama et al., 2016) found a small, insignificant
167 effect with high heterogeneity (Figure 2F).

168 (Insert Figure 2 here)

169 (Insert Figure 3 here)

170 Comparison with norms

75% studies comparing PHIV to norms found significantly worse performance in PHIV (Blanchette, Smith, King, Fernandes-Penney, & Read, 2002; Garcia-Navarro et al., 2013; Martin et al., 2006; Weber et al., 2017). Some studies found varying effect sizes by EF subtype (Garcia-Navarro et al., 2013; Koekkoek, de Sonnevile, Wolfs, Licht, & Geelen, 2008).

Longitudinal changes

The P1104s cohort found significant improvement in inhibition in PHIV and PHU over two years (M. J. Boivin, Chernoff, et al., 2017; M. J. Boivin et al., 2018). Both groups improved in planning; however, PHIV still lagged behind at follow-up (M. J. Boivin et al., 2018). Only PHIV improved on caregiver-reported global EF after one year (M. J. Boivin, Chernoff, et al., 2017). NOVICE found no significant change in working memory in PHIV or PHU over 4 years; however, PHIV deteriorated in set-shifting (Van den Hof et al., 2019). PREDICT found PHIV still had inferior EF to PHU at follow-up (Kerr et al., 2018).

Perinatally acquired HIV on ART compared to perinatally HIV-exposed uninfected

Verbal working memory

Meta-analysis of six studies (PHIV n = 1116; PHEU n = 701) (M. J. Boivin et al., 2018; Debeaudrap et al., 2018; Llorente et al., 2014; Milligan & Cockcroft, 2017; Puthanakit et al., 2013; Smith et al., 2012) found a small, significant effect with high heterogeneity (Figure 4A) and no evidence of publication bias (LFK index = 0.15; no asymmetry).

Visuospatial working memory

Meta-analysis of four studies (PHIV n = 699; PHEU n = 486) (M. J. Boivin et al., 2018; Llorente et al., 2014; Milligan & Cockcroft, 2017; Puthanakit et al., 2013) found a small, significant effect with high heterogeneity (Figure 4B) and evidence of publication bias (LFK index = 1.82; minor asymmetry).

Inhibition

Meta-analysis of three studies (PHIV n = 448; PHEU n = 297) (M. J. Boivin et al., 2018; Milligan, 2016; Nichols, Chernoff, et al., 2016) found a small, significant effect with minimal heterogeneity (Figure 4C) and no evidence of publication bias (LFK index = 0.20; no asymmetry).

Set-shifting

Meta-analysis of three studies (PHIV n = 531; PHEU n = 295) (Llorente et al., 2014; Nichols, Chernoff, et al., 2016; Puthanakit et al., 2013) found no effect with minimal heterogeneity (Figure 4D) and no evidence of publication bias (LFK index = 0.43; no asymmetry).

Planning

Meta-analysis of four studies (PHIV n = 704; PHEU n = 454) (M. J. Boivin et al., 2018; Debeaudrap et al., 2018; Llorente et al., 2014; Nichols et al., 2015) found a small, insignificant effect with high heterogeneity (Figure 4E) and no evidence of publication bias (LFK index = 0.90; no asymmetry).

Global executive function

Meta-analysis of two studies comparing caregiver-reported global EF (PHIV n = 304; PHEU n = 238) (M. J. Boivin et al., 2018; Ezeamama et al., 2016) found a small, insignificant effect with moderate heterogeneity (Figure 4F).

(Insert Figure 4 here)

Longitudinal changes

In CASA, PHIV and PHEU improved similarly in working memory and set-shifting during adolescence (R. Robbins et al., 2018; R. N. Robbins et al., 2019). In P1104s, PHIV and PHEU improved in inhibition and caregiver-reported EF (M. J. Boivin, Chernoff, et al., 2017). In PHACS AMP, PHIV and PHEU improved on set-shifting and inhibition (Malee et al., 2017). WITS found no differences between PHIV and PHEU at 8-years-old or 10-years-old (Llorente et al., 2014).

Perinatally acquired HIV on ART compared to mixed perinatally HIV-exposed uninfected or HIV-unexposed uninfected controls living in HIV-affected households

Verbal working memory

Meta-analysis of six studies (PHIV n = 945; PHEU/PHU n = 1185) (Blanchette et al., 2002; Ene et al., 2016; Foster et al., 2012; Gadow et al., 2012; Sherr, Hensels, Tomlinson, Skeen, & Macedo, 2018) found a small, significant effect with moderate heterogeneity (Figure 5A) and evidence of publication bias (LFK index = -3.98; major asymmetry).

Inhibition

Meta-analysis of four studies (PHIV n = 371; PHEU/PHU n = 163) (Ashby et al., 2015; Foster et al., 2012; Judd et al., 2015; Nagarajan et al., 2012) found no effect with minimal heterogeneity (Figure 5B) and evidence of publication bias (LFK index = -3.04; major asymmetry).

Set-shifting

Meta-analysis of three studies (PHIV n = 492; PHEU/PHU n = 158) (Blanchette et al., 2002; Ene et al., 2016; Judd et al., 2016; Judd et al., 2015) found a small, significant effect with low heterogeneity (Figure 5C) and no evidence of publication bias (LFK index = -0.04; no asymmetry).

Global executive function

Meta-analysis of two studies comparing self-reported global EF problems (PHIV n = 232; PHEU/PHU n = 86) (Ene et al., 2016; Foster et al., 2012) found a small, significant effect with minimal heterogeneity (Figure 5D).

(Insert Figure 5 here)

Longitudinal changes

In an Africa-based cohort, both groups improved with PHIV still having deficits at follow-up (Sherr et al., 2018). A US cohort found no significant changes (Foster et al., 2012). In AALPHI, EF remained similar in both groups at follow-up (Arenas-Pinto et al., 2019).

239 *Perinately HIV-exposed uninfected compared to healthy perinately HIV-unexposed uninfected controls*

240 Verbal working memory

241 Meta-analysis of six studies (PHEU n = 648; PHU n = 624) (Bagenda et al., 2006; M. J. Boivin et al., 1995;
242 Michael J. Boivin et al., 2019; Debeaudrap et al., 2018; Milligan & Cockcroft, 2017; Puthanakit et al., 2013)
243 found no effect with high heterogeneity (Figure 6A) and evidence of publication bias (LFK index = -3.36;
244 major asymmetry).

245 Visuospatial working memory

246 Meta-analysis of six studies (PHEU n = 658; PHU n = 888) (Bagenda et al., 2006; M. J. Boivin et al., 2018;
247 M. J. Boivin et al., 1995; Milligan & Cockcroft, 2017; Puthanakit et al., 2013; M. J. Rotheram-Borus,
248 Tomlinson, Scheffler, Harris, & Nelson, 2017) found no effect with high heterogeneity (Figure 6B) and
249 evidence of publication bias (LFK index = 2.19; major asymmetry).

250 Inhibition

251 Meta-analysis of two studies (PHEU n = 212; PHU n = 211) (M. J. Boivin et al., 2018; Milligan, 2016)
252 found a small, insignificant effect with high heterogeneity (Figure 6C).

253 Planning

254 Meta-analysis of two studies (PHEU n = 191; PHU n = 212) (M. J. Boivin et al., 2018; Debeaudrap et al.,
255 2018) found no effect with moderate heterogeneity (Figure 6D).

256 Global executive function

257 Meta-analysis of two studies assessing caregiver-reported global EF (PHEU n = 238; PHU n = 235) (M. J.
258 Boivin et al., 2018; Ezeamama et al., 2016) found no effect with minimal heterogeneity (Figure 6E).

259 (Insert Figure 6 here)

260 Longitudinal changes

P1104s found significant improvements in inhibition in both groups over a year, with PHEU also improving on caregiver-reported global EF (M. J. Boivin, Chernoff, et al., 2017). Another African cohort found similar EF in both groups at 3-years-old and 5-years-old (M. J. Rotheram-Borus et al., 2018; M. J. Rotheram-Borus et al., 2017). PREDICT found no differences between groups at follow-up (Kerr et al., 2018).

Perinatally acquired HIV subgroup comparisons

Verbal working memory

Meta-analysis of four studies comparing CDC C (more advanced disease) to non-C (C n = 203; non-C n = 523) (Haase et al., 2014; Judd et al., 2016; Llorente et al., 2014; Smith et al., 2012) found a small, significant effect with minimal heterogeneity (Figure 7A) and evidence of publication bias (LFK index = -1.67; minor asymmetry).

Inhibition

Meta-analysis of two studies comparing CDC C to non-C (CDC C n = 73; non-C n = 140) (Haase et al., 2014; Nichols, Chernoff, et al., 2016) found a small negative effect with minimal heterogeneity (Figure 7B).

Set-shifting

Meta-analysis of three studies comparing CDC C to non-C (CDC C n = 135; non-C n = 376) (Llorente et al., 2014; Nichols, Chernoff, et al., 2016) found a small, significant effect with minimal heterogeneity (Figure 7C) and evidence of publication bias (LFK index = -3.44; major asymmetry).

Planning

Meta-analysis of two studies comparing CDC C to non-C (CDC n = 41; non-C n = 49) (Haase et al., 2014; Llorente et al., 2014) found no effect and minimal heterogeneity (Figure 7D).

(Insert Figure 7 here)

Longitudinal changes

In PHACS AMP, CDC C and non-C improved similarly (Malee et al., 2017). In PREDICT, there were no significant changes in the early or deferred ART arms at initial follow-up; later longitudinal analysis revealed three distinct cognitive trajectory phenotypes; only the high-scoring group improved (Patel et al., 2018; Puthanakit et al., 2013).

Behaviourally acquired HIV compared to HIV-negative controls

Set-shifting

Meta-analysis of two studies (BHIV n = 55; HIV-negative n = 47) (Baker et al., 2014; West, 2001) found no effect with moderate heterogeneity (Figure 8).

(Insert Figure 8 here)

Longitudinal changes

ATN 071 found improvement over three years, unrelated to ART initiation timing (Nichols, Bethel, et al., 2016).

Factors associated with executive function

Several potential predictors were examined (Table III). Factors positively associated with EF in ≥ 1 study included: growth parameters; education level; sleep duration; biological parent as caregiver; maternal intelligence; good parenting; socio-economic status (SES); cash transfers; higher immunological markers at ART initiation (M. J. Boivin, Nakasujja, et al., 2017; Brahmabhatt et al., 2017; Foster et al., 2012; Koekkoek et al., 2008; Sherr, Macedo, Tomlinson, Skeen, & Cluver, 2017; Smith et al., 2012). There were inconsistent findings for current disease markers (Bangirana et al., 2016; Kapetanovic et al., 2010; Malee et al., 2017; Martin et al., 2006; Nagarajan et al., 2012; Nichols et al., 2015; Ruel et al., 2012). Factors negatively associated included: past advanced disease and/or encephalopathy (Judd et al., 2015; Malee et al., 2017; Smith et al., 2012; S. Y. Walker, Pierre, Christie, & Chang, 2013); low SES; educational risk (e.g. grade repetition); caregiver depression; latent Toxoplasma infection; attention-deficit/hyperactivity disorder (ADHD) (Burkey et al., 2015; Ene et al., 2016; I. Familiar et al., 2018; I. Familiar et al., 2016; Judd et al., 2015; Malee et al., 2017; Nichols et al., 2015; Patel et al., 2018; R. N. Robbins et al., 2019; Smith et al.,

2012; S. Y. Walker et al., 2013). Some studies found later ART initiation was associated with poorer EF (Benki-Nugent et al., 2016; J. Hoare et al., 2019; Van den Hof et al., 2019). Potential neuroimaging, vascular and immunological markers associated with EF in HIV were identified (Table IV). Positive functional associations with EF in PHIV and/or PHEU (Table V) included: academic achievement; adherence (Garvie et al., 2017; Sirois et al., 2016). In adolescents with BHIV, EF was associated positively with education level, negatively with psychological distress, and inconsistently with current disease markers (Baker et al., 2014; Nichols et al., 2013; Nichols, Bethel, et al., 2016; Salama et al., 2013); EF was not associated with risky behaviour (Baker et al., 2014) (Table VI).

(Insert Table III here)

(Insert Table IV here)

(Insert Table V here)

(Insert Table VI here)

321 ***Interventions affecting executive function***

322 There were eight intervention studies; two pharmacological (Table C, Appendix 2). PREDICT found no
323 effect of early versus delayed ART initiation (Puthanakit et al., 2013). PENTA 11 found no effects after a
324 planned treatment interruption (Ananworanich et al., 2016).

325 One study compared a year-long mediational intervention for sensitising caregivers (MISC) compared to
326 UCOBAC nutrition and hygiene curriculum in PHIV and PHEU pre-schoolers. UCOBAC had fewer
327 caregiver-reported EF problems after one year (Bass et al., 2017; M. J. Boivin, Nakasujja, et al., 2017). A
328 Kenyan study in PHEU 4-8-year-olds found no difference in verbal working memory improvements after 18
329 months of protein-enriched biscuits compared to wheat biscuits (Loo et al., 2017).

330 Three studies (two RCTs; one uncontrolled) tested 1-2 months of computerised cognitive rehabilitation
331 therapy (CCRT) 2-3 sessions/week in school-aged children and adolescents. All found improvements in
332 spatial working memory and planning, but not inhibition or verbal working memory (M. J. Boivin, Busman,
333 et al., 2010; M. J. Boivin, Nakasujja, Sikorskii, Opoka, & Giordani, 2016; Giordani et al., 2015).

334 A pilot RCT in HIV-positive adolescents comparing two months (nine sessions) of mindfulness-based stress
335 reduction (MBSR) to 'Healthy Topics' curriculum found no differences at immediate and 3-month follow-
336 up, except for superior MBSR group accuracy on negative-emotion Stroop immediately post-programme
337 (Webb, Perry-Parrish, Ellen, & Sibinga, 2017).

338 **Discussion**

339 ***Main findings and implications***

340 (Insert Table VII here)

341 Evidence was extremely limited for adolescents with BHIV. Findings suggest a distinct pattern of EF
342 involvement in PHIV (Table VII): verbal and visuospatial working memory were most affected, with
343 smaller effects on planning, inhibition and self-reported global EF, and minimal effects on set-shifting and
344 caregiver-reported global EF. The effect sizes were larger when comparing PHIV on ART to healthy HIV-

345 unaffected controls. They diminished when controls lived in HIV-affected households, with or without
346 perinatal HIV exposure. This suggests that effects are partly due to perinatal HIV exposure and associated
347 psychosocial risks from living in an HIV-affected household. This is supported by the findings that
348 psychosocial resilience factors (e.g. higher SES, cash receipt, good parenting, longer schooling) were
349 associated with better EF (Brahmbhatt et al., 2017; Patel et al., 2018; Rochat et al., 2016; Sherr et al., 2017;
350 Smith et al., 2012).

351 Meta-analyses found no effect of perinatal HIV exposure; however, there was high heterogeneity with
352 negative effects on working memory and inhibition in some contexts and limited evidence for other subtypes
353 (M. J. Boivin et al., 1995; Milligan, 2016; Milligan & Cockcroft, 2017).

354 Effects may differ by context perhaps due to different HIV subtypes (Tyor, Fritz-French, & Nath, 2013) or
355 cumulative neurodevelopmental threats in LMICs (Cluver & Orkin, 2009; Engle & Black, 2008; Mellins &
356 Malee, 2013). EF effects may be related to the specific HIV immunological and virological course
357 (Muenchhoff et al., 2014) with more advanced disease associated with poorer EF (small effects) and slow
358 progressors having similar EF to controls.

359 Current biomarker data suggests both ongoing systemic low-grade inflammation (Foster et al., 2012; J.
360 Hoare et al., 2019; Kim-Chang et al., 2019) and neuroinflammation may be involved in neuronal injury.
361 Both grey matter, particularly frontal (Lewis-de los Angeles et al., 2017), and white matter abnormalities
362 have been associated with poorer EF (J. Hoare et al., 2019; Uban et al., 2015; Van Dalen et al., 2016).
363 Biological risk factors common in HIV infection (e.g. stunting, latent *Toxoplasma* infection) may also
364 contribute (M. J. Boivin, Nakasujja, et al., 2017; Brahmbhatt et al., 2017; Ene et al., 2016).

365 In terms of developmental trajectories, most data suggested similar improvement in PHIV on ART and
366 controls which did not seem to be affected by ART timing (Nichols, Bethel, et al., 2016).

367 Factors positively associated with EF may act as potential targets for psychosocial interventions (e.g.
368 schooling duration, parenting quality, cash transfers, caregiver depression, and adolescent psychological

distress). Interventions tested at different developmental stages have had no or limited effects (M. J. Boivin, Busman, et al., 2010; M. J. Boivin et al., 2016; Giordani et al., 2015).

Limitations

One limitation was the heterogeneity of control groups. Performing separate analyses by control group and EF subtypes might have increased the risk of type 1 errors (Bender et al., 2008). The number of included studies was low in most meta-analyses resulting in less precise estimates.

There were also limitations relating to cross-cultural measurement. Evidence is less robust for non-working memory EF subtypes, possibly because there are fewer cross-culturally validated tasks. Some tasks were used without local validation. Measuring EF subtypes is challenging because tasks often place demands on other EFs and non-EF cognitive processes. Behavioural report measures are subjective (I. Familiar et al., 2016).

The low number of included studies per meta-analysis precluded meta-regression and quantification of moderator effects (*Cochrane Handbook for Systematic Reviews of Interventions*, 2011). Since most studies spanned childhood and adolescence, we could not examine effects at distinct periods. Most studies used facility-based recruitment and some excluded advanced HIV making them less representative of the most vulnerable populations.

Research gaps

More research is needed on non-working memory hot and cool EF, paediatric HAND mechanisms, adolescents with behaviourally acquired HIV, EF-related functional associations (e.g. risky sexual behaviour), and interventions.

Conclusions

This systematic review confirmed that executive function continues to be affected in children and adolescents with perinatal HIV infection despite the use of antiretroviral therapy; however, the evidence is limited for adolescents with behaviourally acquired HIV. Perinatal HIV infection seems to affect working

memory the most with smaller effects on inhibition, set-shifting and planning. Interventions tested so far have shown limited effects. More research on mechanisms and interventions is needed.

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**, **, ** and ** conceptualised the topic. ** wrote the protocol and performed the search. ** screened all records for inclusion. ** and ** each screened half the records for inclusion independently. **, ** and ** chose the final studies for inclusion. ** extracted data and did quality assessments on all included studies. **, ** and ** checked data extraction. ** did independent quality assessments on all included studies. ** analysed the data and drafted the manuscript. **, **, ** and ** critically reviewed the manuscript for intellectual content. All authors assisted with manuscript revision and approved the final draft of the manuscript.

Declaration of interests

The authors have no competing interests to declare.

References

- Alvarez-Bueno, C., Pesce, C., Caverio-Redondo, I., Sanchez-Lopez, M., Martinez-Hortelano, J. A., & Martinez-Vizcaino, V. (2017). The Effect of Physical Activity Interventions on Children's Cognition and Metacognition: A Systematic Review and Meta-Analysis. *J Am Acad Child Adolesc Psychiatry*, 56(9), 729-738. doi:10.1016/j.jaac.2017.06.012
- Ananworanich, J., Melvin, D., Amador, J. T., Childs, T., Medin, G., Boscolo, V., . . . Gibb, D. M. (2016). Neurocognition and quality of life after reinitiating antiretroviral therapy in children randomized to planned treatment interruption. *Aids*, 30(7), 1075-1081. doi:10.1097/qad.0000000000001011
- Anderson, V., Spencer-Smith, M., Coleman, L., Anderson, P., Williams, J., Greenham, M., . . . Jacobs, R. (2010). Children's executive functions: Are they poorer after very early brain insult. *Neuropsychologia*, 48(7), 2041-2050. doi:10.1016/j.neuropsychologia.2010.03.025
- Arenas-Pinto, A., Castro, H., Melvin, D., Le Prevost, M., Foster, C., Sturgeon, K., . . . Judd, A. (2019). *Focused Cognitive Function Testing in Young People with Perinatal HIV in England*. Paper presented at the CROI,

- Seattle, Washington. <https://www.croiconference.org/sessions/focused-cognitive-function-testing-young-people-perinatal-hiv-england>
- Ashby, J., Foster, C., Garvey, L., Wan, T., Allsop, J., Parameswaran, Y., . . . Winston, A. (2015). Cerebral function in perinatally HIV-infected young adults and their HIV-uninfected sibling controls. *HIV Clin Trials*, 16(2), 81-87. doi:10.1179/1528433614z.00000000003
- Bagenda, D., Nassali, A., Kalyesubula, I., Sherman, B., Drotar, D., Boivin, M. J., & Olness, K. (2006). Health, neurologic, and cognitive status of HIV-infected, long-surviving, and antiretroviral-naïve Ugandan children. *Pediatrics*, 117(3), 729-740. doi:10.1542/peds.2004-2699
- Baker, L. M., Paul, R. H., Heaps, J. H., Westerhaus, E., Chang, J. Y., Williams, S., . . . Ances, B. M. (2014). Impact of human immunodeficiency virus on neurocognition and risky behaviors in young adults. *J Neurovirol*, 20(5), 466-473. doi:10.1007/s13365-014-0264-4
- Bangirana, P., Boivin, M. J., Ruel, T., & Achan, J. (2015). *Long term effect of PI based ART versus NNRTI based ART on neuropsychological functioning in children*. Paper presented at the International Workshop on HIV Pediatrics, Vancouver, Canada. http://regist2.virology-education.com/abstractbook/2015_8.pdf
- Bangirana, P., Giordani, B., John, C. C., Page, C., Opoka, R. O., & Boivin, M. J. (2009). Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors. *Journal of Developmental and Behavioral Pediatrics*, 30(4), 310-318. doi:10.1097/DBP.0b013e3181b0f01b
- Bangirana, P., Ruel, T., Boivin, M. J., Satish, P., Giron, L., Sikorskii, A., . . . Achan, J. (2016). *Subtype A is not associated with poorer neurocognitive outcomes than subtype D in HIV-infected children receiving antiretroviral therapy*. Paper presented at the International Workshop on HIV Pediatrics, Durban, South Africa. http://www.infectiousdiseasesonline.com/wp-content/uploads/2016/07/8th-HIVPediatrics_abstractbook_web.pdf
- Bass, J. K., Opoka, R., Familiar, I., Nakasujja, N., Sikorskii, A., Awadu, J., . . . Boivin, M. (2017). Randomized controlled trial of caregiver training for HIV-infected child neurodevelopment and caregiver well being. *Aids*, 31(13), 1877-1883. doi:10.1097/qad.0000000000001563
- Bender, R., Bunce, C., Clarke, M., Gates, S., Lange, S., Pace, N. L., & Thorlund, K. (2008). Attention should be given to multiplicity issues in systematic reviews. *J Clin Epidemiol*, 61(9), 857-865. doi:10.1016/j.jclinepi.2008.03.004
- Benki-Nugent, S., Wamalwa, D., Laboso, T., Tamasha, N., Otieno, M., Bangirana, P., . . . John-Stewart, G. (2016). *HIV-infected children who initiated ART during infancy (early ART) have improved neurocognitive outcomes compared with late-treated children*. Paper presented at the International Workshop on HIV Pediatrics, Durban, South Africa. http://www.infectiousdiseasesonline.com/wp-content/uploads/2016/07/8th-HIVPediatrics_abstractbook_web.pdf
- Bergman Nutley, S., Darki, F., & Klingberg, T. (2014). Music practice is associated with development of working memory during childhood and adolescence. *Frontiers in Human Neuroscience*, 7. doi:10.3389/fnhum.2013.00926

- Best, J. R., Miller, P. H., & Naglieri, J. A. (2011). Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. *Learning and Individual Differences*, 21(4), 327-336. doi:10.1016/j.lindif.2011.01.007
- Bisiacchi, P., Mento, G., Tarantino, V., & Burlina, A. (2018). Subclinical executive function impairment in children with asymptomatic, treated phenylketonuria: A comparison with children with immunodeficiency virus. *Cognitive Neuropsychology*, 35(3-4), 200-208. doi:10.1080/02643294.2017.1396207
- Blakemore, S. J., & Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *Journal of Child Psychology and Psychiatry*, 47(3-4), 296-312. doi:10.1111/j.1469-7610.2006.01611.x
- Blanchette, N., Smith, M. L., King, S., Fernandes-Penney, A., & Read, S. (2002). Cognitive development in school-age children with vertically transmitted HIV infection. *Developmental Neuropsychology*, 21(3), 223-241. doi:10.1207/s15326942dn2103_1
- Blokhuys, C., Peeters, C. F. W., Cohen, S., Scherpbier, H. J., Kuijpers, T. W., Reiss, P., . . . Pajkrt, D. (2019). Systemic and intrathecal immune activation in association with cerebral and cognitive outcomes in paediatric HIV. *Sci Rep*, 9(1), 8004. doi:10.1038/s41598-019-44198-z
- Boivin, M. J., Barlow-Mosha, L., Chernoff, M. C., Laughton, B., Zimmer, B., Joyce, C., . . . Team, I. P. S. (2018). Neuropsychological performance in African children with HIV enrolled in a multisite antiretroviral clinical trial. *Aids*, 32(2), 189-204. doi:10.1097/qad.0000000000001683
- Boivin, M. J., Busman, R. A., Parikh, S. M., Bangirana, P., Page, C. F., Opoka, R. O., & Giordani, B. (2010). A Pilot Study of the Neuropsychological Benefits of Computerized Cognitive Rehabilitation in Ugandan Children With HIV. *Neuropsychology*, 24(5), 667-673. doi:10.1037/a0019312
- Boivin, M. J., Chernoff, M., Laughton, B., Bwakura-Dangarembizi, M., Kamthunzi, P., Barlow-Mosha, L., . . . Palumbo, P. (2017). *Neuropsychological outcomes in a two year African-based pediatric observational study*. Paper presented at the CROI, Seattle, Washington, US.
http://www.croiconference.org/sites/default/files/posters-2017/826_Boivin.pdf
- Boivin, M. J., Chernoff, M., Laughton, B., Zimmer, B., Joyce, C., Barlow-Mosha, L., . . . Palumbo, P. (2018). *African Multi-Site 2-Year Study of Neurocognition in HIV Infected/Affected Children*. Paper presented at the CROI, Seattle, Washington. <https://www.croiconference.org/sessions/african-multi-site-2-year-study-neurocognition-hiv-infectedaffected-children>
- Boivin, M. J., Davies, A. G., Mokili, J. K. L., Green, S. D. R., Giordani, B., & Cutting, W. A. M. (1995). A PRELIMINARY EVALUATION OF THE COGNITIVE AND MOTOR EFFECTS OF PEDIATRIC HIV-INFECTION IN ZAIRIAN CHILDREN. *Health Psychology*, 14(1), 13-21. doi:10.1037/0278-6133.14.1.13
- Boivin, M. J., Maliwichi-Senganimalunje, L., Ogwang, L. W., Kawalazira, R., Sikorskii, A., Familiar-Lopez, I., . . . Fowler, M. G. (2019). Neurodevelopmental effects of ante-partum and post-partum antiretroviral exposure in HIV-exposed and uninfected children versus HIV-unexposed and uninfected children in Uganda and Malawi: a prospective cohort study. *The Lancet HIV*. doi:10.1016/S2352-3018(19)30083-9
- Boivin, M. J., Nakasujja, N., Familiar-Lopez, I., Murray, S. M., Sikorskii, A., Awadu, J., . . . Bass, J. K. (2017). Effect of Caregiver Training on the Neurodevelopment of HIV-Exposed Uninfected Children and Caregiver Mental

- Health: A Ugandan Cluster-Randomized Controlled Trial. *Journal of Developmental and Behavioral Pediatrics*, 38(9), 753-764. doi:10.1097/DBP.0000000000000510
- Boivin, M. J., Nakasujja, N., Sikorskii, A., Opoka, R. O., & Giordani, B. (2016). A Randomized Controlled Trial to Evaluate if Computerized Cognitive Rehabilitation Improves Neurocognition in Ugandan Children with HIV. *AIDS Res Hum Retroviruses*, 32(8), 743-755. doi:10.1089/aid.2016.0026
- Boivin, M. J., Ruel, T. D., Boal, H. E., Bangirana, P., Cao, H., Eller, L. A., . . . Wong, J. K. (2010). HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children. *Aids*, 24(8), 1163-1170. doi:10.1097/qad.0b013e3283389dcc
- Brahmbhatt, H., Boivin, M., Ssempijja, V., Kagaayi, J., Kigozi, G., Serwadda, D., . . . Gray, R. H. (2017). Impact of HIV and Atiretroviral Therapy on Neurocognitive Outcomes Among School-Aged Children. *Journal of Acquired Immune Deficiency Syndromes*, 75(1), 1-8. doi:10.1097/QAI.0000000000001305
- Burkey, M. D., Murray, S. M., Bangirana, P., Familiar, I., Opoka, R. O., Nakasujja, N., . . . Bass, J. K. (2015). Executive function and attention-deficit/hyperactivity disorder in Ugandan children with perinatal HIV exposure. *Global Mental Health*, 2, e4. doi:10.1017/gmh.2015.2
- Casey, B. J., & Caudle, K. (2013). The Teenage Brain: Self Control. *Current Directions in Psychological Science*, 22(2), 82-87. doi:10.1177/0963721413480170
- Cerrillo-Urbina, A. J., Garcia-Hermoso, A., Sanchez-Lopez, M., Pardo-Guijarro, M. J., Santos Gomez, J. L., & Martinez-Vizcaino, V. (2015). The effects of physical exercise in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis of randomized control trials. *Child Care Health Dev*, 41(6), 779-788. doi:10.1111/cch.12255
- Chahroudi, A., Wagner, T. A., & Persaud, D. (2018). CNS Persistence of HIV-1 in Children: the Untapped Reservoir. *Curr HIV/AIDS Rep*, 15(5), 382-387. doi:10.1007/s11904-018-0412-1
- Cluver, L., & Orkin, M. (2009). Cumulative risk and AIDS-orphanhood: interactions of stigma, bullying and poverty on child mental health in South Africa. *Social Science & Medicine*, 69(8), 1186-1193. doi:10.1016/j.socscimed.2009.07.033
- Cochrane Handbook for Systematic Reviews of Interventions*. (2011). (J. P. Higgins & S. Green Eds. 5.1.0 ed.): The Cochrane Collaboration.
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences, Second Edition*: Lawrence Erlbaum Associates.
- Cohen, S., Ter Stege, J. A., Geurtsen, G. J., Scherpbier, H. J., Kuijpers, T. W., Reiss, P., . . . Pajkrt, D. (2015). Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. *Clin Infect Dis*, 60(7), 1111-1119. doi:10.1093/cid/ciu1144
- Crowell, C. S., Malee, K. M., Yogeve, R., & Muller, W. J. (2014). Neurologic disease in HIV-infected children and the impact of combination antiretroviral therapy. *Reviews in Medical Virology*, 24(5), 316-331. doi:10.1002/rmv.1793
- Dahl, V., Gisslen, M., Hagberg, L., Peterson, J., Shao, W., Spudich, S., . . . Palmer, S. (2013). An Example of Genetically Distinct HIV Type 1 Variants in Cerebrospinal Fluid and Plasma During Suppressive Therapy. *J Infect Dis*, 209(10), 1618-1622. doi:10.1093/infdis/jit805

- De Pereira, A. P. A., & Cunha, A. P. (2012). Processing speed and working memory in children with HIV. *International Journal of Psychology*, 47, 565-565.
- Debeaudrap, P., Bodeau-Livinec, F., Pasquier, E., Germanaud, D., Ndiang, S. T., Nlend, A. N., . . . Grp, A. N.-P. S. (2018). Neurodevelopmental outcomes in HIV-infected and uninfected African children. *Aids*, 32(18), 2749-2757. doi:10.1097/qad.0000000000002023
- Diamond, A., Barnett, W. S., Thomas, J., & Munro, S. (2007). Preschool program improves cognitive control. *Science*, 318(5855), 1387-1388. doi:10.1126/science.1151148
- Doi, S. A., Barendregt, J. J., Khan, S., Thalib, L., & Williams, G. M. (2015a). Advances in the meta-analysis of heterogeneous clinical trials II: The quality effects model. *Contemporary Clinical Trials*, 45(Pt A), 123-129. doi:10.1016/j.cct.2015.05.010
- Doi, S. A., Barendregt, J. J., Khan, S., Thalib, L., & Williams, G. M. (2015b). Simulation Comparison of the Quality Effects and Random Effects Methods of Meta-analysis. *Epidemiology*, 26(4), e42-44. doi:10.1097/ede.0000000000000289
- Doi, S. A., & Thalib, L. (2008). A quality-effects model for meta-analysis. *Epidemiology*, 19(1), 94-100. doi:10.1097/EDE.0b013e31815c24e7
- Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non- randomised studies of health care interventions. *J Epidemiol Community Health*, 52, 377-384. doi:10.1136/jech.52.6.377
- Eckard, A. R., Rosebush, J. C., O'Riordan, M. A., Graves, C. C., Alexander, A., Grover, A. K., . . . McComsey, G. A. (2017). Neurocognitive dysfunction in HIV-infected youth: investigating the relationship with immune activation. *Antivir Ther*, 22(8), 669-680. doi:10.3851/imp3157
- Ene, L., Marcotte, T. D., Umlauf, A., Grancea, C., Temereanca, A., Bharti, A., . . . Ruta, S. M. (2016). Latent toxoplasmosis is associated with neurocognitive impairment in young adults with and without chronic HIV infection. *J Neuroimmunol*, 299, 1-7. doi:10.1016/j.jneuroim.2016.08.003
- Engle, P. L., & Black, M. M. (2008). The Effect of Poverty on Child Development and Educational Outcomes. *Ann N Y Acad Sci*, 1136(1), 243-256. doi:10.1196/annals.1425.023
- Ezeamama, A. E., Kizza, F. N., Zalwango, S. K., Nkwata, A. K., Zhang, M., Rivera, M. L., . . . Whalen, C. C. (2016). Perinatal HIV Status and Executive Function During School-Age and Adolescence: A Comparative Study of Long-Term Cognitive Capacity Among Children From a High HIV Prevalence Setting. *Medicine (Baltimore)*, 95(17), e3438. doi:10.1097/md.0000000000003438
- Familiar, I., Chernoff, M., Ruisenor-Escudero, H., Laughton, B., Joyce, C., Fairlie, L., . . . Boivin, M. (2018). *Caregiver depression and child neuropsychological outcomes in an observational study carried out in four sub-Saharan countries*. Paper presented at the Aids, Amsterdam, Netherlands.
- http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427
- Familiar, I., Nakasujja, N., Bass, J., Sikorskii, A., Murray, S. M., Ruisenor-Escudero, H., . . . Boivin, M. J. (2016). Caregivers' depressive symptoms and parent-report of child executive function among young children in Uganda. *Learning and Individual Differences*, 46, 17-24. doi:10.1016/j.lindif.2015.01.012

- Foster, S. B., Lu, M., Glaze, D. G., Reuben, J. M., Harris, L. L., Cohen, E. N., . . . Shearer, W. T. (2012). Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. *Clinical Immunology*, 144(1), 13-23. doi:10.1016/j.clim.2012.04.004
- Furuya-Kanamori, L., Barendregt, J. J., & Doi, S. A. R. (2018). A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid Based Healthc*, 16(4), 195-203. doi:10.1097/xe.0000000000000141
- Gadow, K. D., Angelidou, K., Chernoff, M., Williams, P. L., Heston, J., Hodge, J., & Nachman, S. (2012). Longitudinal study of emerging mental health concerns in youth perinatally infected with HIV and peer comparisons. *J Dev Behav Pediatr*, 33(6), 456-468. doi:10.1097/DBP.0b013e31825b8482
- Garcia-Navarro, C., Gonzalez-Tome, M. I., Zamora, B., Navarro Gomez, M., Cortes, L., Escosa, M., . . . Lopez, C. (2013). *Attentional Deficits in a Paediatric HIV-cohort*. NeuroCoRISpeS. Paper presented at the European AIDS Conference, Brussels, Belgium. <http://www.abstractserver.com/eacsabstractarchive/>
- Garvie, P. A., Brummel, S. S., Allison, S. M., Malee, K. M., Mellins, C. A., Wilkins, M. L., . . . Nichols, S. L. (2017). Roles of Medication Responsibility, Executive and Adaptive Functioning in Adherence for Children and Adolescents With Perinatally Acquired HIV. *Pediatr Infect Dis J*, 36(8), 751-757. doi:10.1097/inf.0000000000001573
- Giordani, B., Novak, B., Sikorskii, A., Bangirana, P., Nakasujja, N., Winn, B. M., & Boivin, M. J. (2015). Designing and evaluating Brain Powered Games for cognitive training and rehabilitation in at-risk African children. *Global Mental Health*, 2. doi:10.1017/gmh.2015.5
- Haase, V. G., Nicolau, N. C., Viana, V. N., Barreto, G. d. V., & Pinto, J. A. (2014). Executive function and processing speed in Brazilian HIV-infected children and adolescents. *Dementia & Neuropsychologia*, 8(1), 32-39.
- Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. San Diego, CA: Academic Press.
- Hoare, J., Fouche, J. P., Spottiswoode, B., Donald, K., Philipps, N., Bezuidenhout, H., . . . Stein, D. (2012). A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve "slow progressors". *J Neurovirol*, 18(3), 205-212. doi:10.1007/s13365-012-0099-9
- Hoare, J., Heany, S. J., Fouche, J. P., Phillips, N., Joska, J. A., Myer, L., . . . Stein, D. J. (2019). Initiation of antiretroviral therapy after the critical neuronal developmental period of the second postnatal year affects white matter microstructure in adolescents living with HIV. *J Neurovirol*. doi:10.1007/s13365-018-0712-7
- Hoare, J., Myer, L., Heany, S., Fouche, J. P., Phillips, N., Zar, H., & Stein, D. (2019). *Systemic inflammation and structural brain changes in perinatally HIV+ adolescents*. Paper presented at the CROI, Seattle, Washington. <https://www.croiconference.org/sessions/systemic-inflammation-and-structural-brain-changes-perinatally-hiv-adolescents>
- Hoare, J., Phillips, N., Joska, J. A., Paul, R., Donald, K. A., Stein, D. J., & Thomas, K. G. (2016). Applying the HIV-associated neurocognitive disorder diagnostic criteria to HIV-infected youth. *Neurology*, 87(1), 86-93. doi:10.1212/wnl.0000000000002669
- Holmes, J., Gathercole, S. E., & Dunning, D. L. (2009). Adaptive training leads to sustained enhancement of poor working memory in children. *Dev Sci*, 12(4), F9-15. doi:10.1111/j.1467-7687.2009.00848.x
- Hooper, P., Jutai, J. W., Strong, G., & Russell-Minda, E. (2008). Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Canadian Journal of Ophthalmology*, 43(2), 180-187. doi:10.3129/i08-001

- Jacobs, R., Harvey, A. S., & Anderson, V. (2007). Executive Function Following Focal Frontal Lobe Lesions: Impact of Timing of Lesion on Outcome. *Cortex*, 43(6), 792-805. doi:10.1016/S0010-9452(08)70507-0
- James, A. N., & Ittyerah, M. (2016). An assessment of WISC-IIIUK on children with HIV infection. *Journal of Health Psychology*, 21(10), 2386-2397. doi:10.1177/1359105315577118
- Judd, A., Le Prevost, M., Melvin, D., Arenas-Pinto, A., Parrott, F., Winston, A., . . . Gibb, D. M. (2016). Cognitive Function in Young Persons with and Without Perinatal HIV in the AALPHI Cohort in England: Role of Non-HIV-Related Factors. *Clinical Infectious Diseases*, 63(10), 1380-1387. doi:10.1093/cid/ciw568
- Judd, A., Nunn, A., Le Prevost, M., Sturgeon, K., Gibb, D. M., Arenas-Pinto, A., . . . Winston, A. (2015). Neurocognitive function in perinatally HIV-infected young people and HIV-negative siblings in England. *Hiv Medicine*, 16, 9. doi:10.1111/hiv.12264
- Kamijo, K., Pontifex, M. B., O'Leary, K. C., Scudder, M. R., Wu, C., Castelli, D. M., & Hillman, C. H. (2011). The effects of an afterschool physical activity program on working memory in preadolescent children. *Dev Sci*, 14(5), 1046-1058. doi:10.1111/j.1467-7687.2011.01054.x
- Kapetanovic, S., Griner, R., Zeldow, B., Nichols, S., Leister, E., Gelbard, H. A., . . . Williams, P. L. (2014). Biomarkers and neurodevelopment in perinatally HIV-infected or exposed youth: a structural equation model analysis. *Aids*, 28(3), 355-364. doi:10.1097/qad.0000000000000072
- Kapetanovic, S., Leister, E., Nichols, S., Miller, T., Tassiopoulos, K., Hazra, R., . . . Williams, P. L. (2010). Relationships between markers of vascular dysfunction and neurodevelopmental outcomes in perinatally HIV-infected youth. *Aids*, 24(10), 1481-1491. doi:10.1097/QAD.0b013e32833a241b
- Kerr, S. J., Puthanakit, T., Thongpaibul, K., Malee, K. M., Ly, P. S., Suwanlerk, T., . . . Mellins, C. A. (2018). *Increased risk of executive, working memory, and emotional-behavioral problems among virologically well-controlled perinatally HIV-infected adolescents in Thailand and Cambodia*. Paper presented at the Aids, Amsterdam, Netherlands. http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427
- Kim-Chang, J. J., Loop, M. S., Donovan, K., Hong, S., Fischer, B., Venturi, G., . . . Sleasman, J. W. (2019). *SCD14, SICAM-1, and SVCAM-1 correlate with neurocognitive function in youth with HIV*. Paper presented at the CROI, Seattle, Washington. <https://www.croiconference.org/sessions/scd14-sicam-1-and-svcam-1-correlate-neurocognitive-function-youth-hiv>
- Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., . . . Westerberg, H. (2005). Computerized training of working memory in children with ADHD--a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*, 44(2), 177-186. doi:10.1097/00004583-200502000-00010
- Koekkoek, S., de Sonnevile, L. M., Wolfs, T. F., Licht, R., & Geelen, S. P. (2008). Neurocognitive function profile in HIV-infected school-age children. *European Journal of Paediatric Neurology*, 12(4), 290-297. doi:10.1016/j.ejpn.2007.09.002
- Koike, S., Hardy, R., & Richards, M. (2015). Adolescent self-control behavior predicts body weight through the life course: a prospective birth cohort study. *International Journal Of Obesity*, 40, 71. doi:10.1038/ijo.2015.213
- Lakes, K. D., & Hoyt, W. T. (2004). Promoting self-regulation through school-based martial arts training. *J Appl Dev Psychol*, 25(3), 283-302. doi:10.1016/j.appdev.2004.04.002

- Lechenadec, J., Benmeharek, Y., Meyer, L., Warszawski, J., Douard, D., Monpoux, F., . . . Blanche, S. (2007). Long-Term Nonprogression of HIV Infection in Children: Evaluation of the ANRS Prospective French Pediatric Cohort. *Clinical Infectious Diseases*, 45(6), 785-794. doi:10.1086/521165
- Lewis-de los Angeles, C. P., Williams, P. L., Huo, Y., Wang, S. D., Uban, K. A., Herting, M. M., . . . Wang, L. (2017). Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: Associations with HIV disease severity, substance use, and cognition. *Brain Behav Immun*, 62, 100-109. doi:10.1016/j.bbi.2017.01.004
- Linn, K., Fay, A., Meddles, K., Isbell, S., Lin, P. N., Thair, C., . . . Mar, S. S. (2015). HIV-Related Cognitive Impairment of Orphans in Myanmar With Vertically Transmitted HIV Taking Antiretroviral Therapy. *Pediatric Neurol*, 53(6), 485-490.e481. doi:10.1016/j.pediatrneurol.2015.08.004
- Llorente, A. M., Brouwers, P., Leighty, R., Malee, K., Smith, R., Harris, L., . . . Chase, C. (2014). An analysis of select emerging executive skills in perinatally HIV-1-infected children. *Applied Neuropsychology: Child*, 3(1), 10-25. doi:10.1080/21622965.2012.686853
- Loo, K. K., Rizzo, S., Chen, Q. L., Weiss, R. E., Sugar, C. A., Ettyang, G., . . . Neumann, C. G. (2017). Effects of biscuit-type feeding supplementation on the neurocognitive outcomes of HIV-affected school-age children: a randomized, double-blind, controlled intervention trial in Kenya. *Family Medicine and Community Health*, 5(4), 245-258. doi:10.15212/fmch.2017.0130
- Maganlal, U. (2013). *Executive function performance in HIV positive adolescents on anti-retroviral treatment in Johannesburg, South Africa*. (M.A. Masters), University of the Witwatersrand, Retrieved from <http://wiredspace.wits.ac.za/bitstream/handle/10539/13960/U%20Maganlal%20-%20Executive%20Function%20in%20HIV%20Positive%20Adolescents%20Final%20Sep%202013.pdf?sequence=3> Available from OCLC WorldCat database.
- Malee, K. M., Chernoff, M. C., Sirois, P. A., Williams, P. L., Garvie, P. A., Kammerer, B. L., . . . Nichols, S. L. (2017). Impact of Perinatally Acquired HIV Disease Upon Longitudinal Changes in Memory and Executive Functioning. *Journal of Acquired Immune Deficiency Syndromes*, 75(4), 455-464. doi:10.1097/qai.0000000000001441
- Martin, S. C., Wolters, P. L., Toledo-Tamula, M. A., Zeichner, S. L., Hazra, R., & Civitello, L. (2006). Cognitive Functioning in School-Aged Children With Vertically Acquired HIV Infection Being Treated With Highly Active Antiretroviral Therapy (HAART). *Developmental Neuropsychology*, 30(2), 633-657. doi:10.1207/s15326942dn3002_1
- Mellins, C. A., & Malee, K. M. (2013). Understanding the mental health of youth living with perinatal HIV infection: lessons learned and current challenges. *J Int AIDS Soc*, 16(18593). doi:10.7448/IAS.16.1.18593
- Miller, M., Nevado-Montenegro, A. J., & Hinshaw, S. P. (2012). Childhood executive function continues to predict outcomes in young adult females with and without childhood-diagnosed ADHD. *J Abnorm Child Psychol*, 40(5), 657-668. doi:10.1007/s10802-011-9599-y
- Milligan, R. (2016). *A comparison of working memory profiles in HIV-infected and HIV-exposed uninfected children*. (PhD Doctoral thesis), University of the Witwatersrand, Available from OCLC WorldCat database.

- Milligan, R., & Cockcroft, K. (2017). Working Memory Profiles in HIV-Exposed, Uninfected and HIV-Infected Children: A Comparison with Neurotypical Controls. *Frontiers in Human Neuroscience*, 11, 13. doi:10.3389/fnhum.2017.00348
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology*, 41(1), 49-100. doi:10.1006/cogp.1999.0734
- Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., . . . Caspi, A. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences*, 108(7), 2693-2698. doi:10.1073/pnas.1010076108
- Moreno, S., Bialystok, E., Barac, R., Schellenberg, E. G., Cepeda, N. J., & Chau, T. (2011). Short-term music training enhances verbal intelligence and executive function. *Psychol Sci*, 22(11), 1425-1433. doi:10.1177/0956797611416999
- Muenchhoff, M., Prendergast, A. J., & Goulder, P. J. R. (2014). Immunity to HIV in Early Life. *Frontiers in Immunology*, 5(391). doi:10.3389/fimmu.2014.00391
- Nachman, S., Chernoff, M., Williams, P., Hodge, J., Heston, J., & Gadow, K. D. (2012). Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth. *Archives of Pediatrics & Adolescent Medicine*, 166(6), 528-535. doi:10.1001/archpediatrics.2011.1785
- Nagarajan, R., Sarma, M. K., Thomas, M. A., Chang, L., Natha, U., Wright, M., . . . Keller, M. A. (2012). Neuropsychological function and cerebral metabolites in HIV-infected youth. *Journal of Neuroimmune Pharmacology*, 7(4), 981-990. doi:10.1007/s11481-012-9407-7
- Nichols, S. L., Bethel, J., Garvie, P. A., Patton, D. E., Thornton, S., Kapogiannis, B. G., . . . Woods, S. P. (2013). Neurocognitive Functioning in Antiretroviral Therapy-Naive Youth With Behaviorally Acquired Human Immunodeficiency Virus. *Journal of Adolescent Health*, 53(6), 763-771. doi:10.1016/j.jadohealth.2013.07.006
- Nichols, S. L., Bethel, J., Kapogiannis, B. G., Li, T., Woods, S. P., Patton, E. D., . . . Garvie, P. A. (2016). Antiretroviral treatment initiation does not differentially alter neurocognitive functioning over time in youth with behaviorally acquired HIV. *J Neurovirol*, 22(2), 218-230. doi:10.1007/s13365-015-0389-0
- Nichols, S. L., Brummel, S. S., Smith, R. A., Garvie, P. A., Hunter, S. J., Malee, K. M., . . . Mellins, C. A. (2015). Executive Functioning in Children and Adolescents With Perinatal HIV Infection. *Pediatr Infect Dis J*, 34(9), 969-975. doi:10.1097/inf.0000000000000809
- Nichols, S. L., Chernoff, M. C., Malee, K. M., Sirois, P. A., Woods, S. P., Williams, P. L., . . . Kammerer, B. (2016). Executive Functioning in Children and Adolescents With Perinatal HIV Infection and Perinatal HIV Exposure. *J Pediatric Infect Dis Soc*, 5(suppl 1), S15-s23. doi:10.1093/jpids/piw049
- Ofori-Mante, J. A., Kaul, A., Rigaud, M., Fidelia, A., Rochford, G., Krasinski, K., . . . Borkowsky, W. (2007). Natural history of HIV infected pediatric long-term or slow progressor population after the first decade of life. *Pediatr Infect Dis J*, 26(3), 217-220.
- Patel, P. B., Apornpong, T., Kerr, S. J., Puthanakit, T., Thongpibul, K., Kosalaraksa, P., . . . Group, O. b. o. t. P. R. S. (2018). Group Based Trajectory Analysis of Cognitive Outcomes in Children with Perinatal HIV. *BioRxiv*. doi:10.1101/398339

- Phillips, N. J., Hoare, J., Stein, D. J., Myer, L., Zar, H. J., & Thomas, K. G. F. (2018). HIV-associated cognitive disorders in perinatally infected children and adolescents: a novel composite cognitive domains score. *AIDS Care*, 30(sup1), 8-16. doi:10.1080/09540121.2018.1466982
- Poon, K. (2017). Hot and Cool Executive Functions in Adolescence: Development and Contributions to Important Developmental Outcomes. *Front Psychol*, 8, 2311-2311. doi:10.3389/fpsyg.2017.02311
- Prencipe, A., Kesek, A., Cohen, J., Lamm, C., Lewis, M. D., & Zelazo, P. D. (2011). Development of hot and cool executive function during the transition to adolescence. *Journal of Experimental Child Psychology*, 108(3), 621-637. doi:10.1016/j.jecp.2010.09.008
- Puthanakit, T., Ananworanich, J., Vonthanak, S., Kosalaraksa, P., Hansudewechakul, R., Lugt, J., . . . Wongsawat, J. (2013). Cognitive function and neurodevelopmental outcomes in HIV-infected Children older than 1 year of age randomized to early versus deferred antiretroviral therapy: the PREDICT neurodevelopmental study. *Pediatr Infect Dis J*, 32. doi:10.1097/INF.0b013e31827fb19d
- Ravindran, O., Rani, M., & Priya, G. (2014). Cognitive deficits in HIV infected children. *Indian Journal of Psychological Medicine*, 36(3), 255-259. doi:10.4103/0253-7176.135373
- Robbins, R., Bucek, A., Raymond, J., Nguyen, N., Dolezal, C., Abrams, E., . . . Mellins, C. A. (2018). *Neurocognitive outcomes among perinatally-HIV infected young adults*. Paper presented at the Aids, Amsterdam, Netherlands. http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427
- Robbins, R. N., Zimmerman, R., Korich, R., Raymond, J., Dolezal, C., Choi, C. J., . . . Mellins, C. A. (2019). Longitudinal trajectories of neurocognitive test performance among individuals with perinatal HIV-infection and -exposure: adolescence through young adulthood. *AIDS Care*, 1-9. doi:10.1080/09540121.2019.1626343
- Rochat, T. J., Houle, B., Stein, A., Coovadia, H., Coutsooudis, A., Desmond, C., . . . Bland, R. M. (2016). Exclusive Breastfeeding and Cognition, Executive Function, and Behavioural Disorders in Primary School-Aged Children in Rural South Africa: A Cohort Analysis. *PLoS Medicine*, 13(6), e1002044. doi:10.1371/journal.pmed.1002044
- Rosenberg, M., Pettifor, A., Duta, M., Demeyere, N., Wagner, R. G., Selin, A., . . . Kahn, K. (2018). Executive function associated with sexual risk in young South African women: Findings from the HPTN 068 cohort. *PLoS One*, 13(4), 14. doi:10.1371/journal.pone.0195217
- Rotheram-Borus, M. J., Tomlinson, M., le Roux, I., Weichle, T., Stewart, J., Gordon, S., & Lin, C. (2018). *Outcomes of South African mothers living with HIV (MLH) and their children compared to neighborhood peer mothers without HIV (MWOH) and their children over five years*. Paper presented at the Aids, Amsterdam, Netherlands. http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427
- Rotheram-Borus, M. J., Tomlinson, M., Scheffler, A., Harris, D. M., & Nelson, S. (2017). Adjustment of a Population of South African Children of Mothers Living With/and Without HIV Through Three Years Post-Birth. *AIDS Behav*, 21(6), 1601-1610. doi:10.1007/s10461-016-1436-4
- Ruel, T. D., Boivin, M. J., Boal, H. E., Bangirana, P., Charlebois, E., Havlir, D. V., . . . Wong, J. K. (2012). Neurocognitive and Motor Deficits in HIV-Infected Ugandan Children With High CD4 Cell Counts. *Clinical Infectious Diseases*, 54(7), 1001-1009. doi:10.1093/cid/cir1037

- Ruisenor-Escudero, H., Familiar, I., Nakasujja, N., Bangirana, P., Opoka, R., Giordani, B., & Boivin, M. (2015). Immunological correlates of behavioral problems in school-aged children living with HIV in Kayunga, Uganda. *Global Mental Health*, 2, e9. doi:10.1017/gmh.2015.7
- Salama, C., Morris, M., Armistead, L., Koenig, L. J., Demas, P., Ferdon, C., & Bachanas, P. (2013). Depressive and conduct disorder symptoms in youth living with HIV: the independent and interactive roles of coping and neuropsychological functioning. *AIDS Care*, 25(2), 160-168. doi:10.1080/09540121.2012.687815
- Sawyer, S. M., Azzopardi, P. S., Wickremarathne, D., & Patton, G. C. (2018). The age of adolescence. *The Lancet Child & Adolescent Health*, 2(3), 223-228. doi:10.1016/S2352-4642(18)30022-1
- Schlam, T. R., Wilson, N. L., Shoda, Y., Mischel, W., & Ayduk, O. (2013). Preschoolers' Delay of Gratification Predicts their Body Mass 30 Years Later. *J Pediatr*, 162(1), 90-93. doi:10.1016/j.jpeds.2012.06.049
- Sherr, L., Hensels, I. S., Tomlinson, M., Skeen, S., & Macedo, A. (2018). Cognitive and physical development in HIV-positive children in South Africa and Malawi: A community-based follow-up comparison study. *Child Care Health Dev*, 44(1), 89-98. doi:10.1111/cch.12533
- Sherr, L., Macedo, A., Tomlinson, M., Skeen, S., & Cluver, L. D. (2017). Could cash and good parenting affect child cognitive development? A cross-sectional study in South Africa and Malawi. *BMC Pediatrics*, 17(1). doi:10.1186/s12887-017-0883-z
- Sirois, P. A., Chernoff, M. C., Malee, K. M., Garvie, P. A., Harris, L. L., Williams, P. L., . . . Nichols, S. L. (2016). Associations of Memory and Executive Functioning With Academic and Adaptive Functioning Among Youth With Perinatal HIV Exposure and/or Infection. *J Pediatric Infect Dis Soc*, 5(Suppl 1), S24-S32. doi:10.1093/jpids/piw046
- Smalley, S. L., Kitil, M. J., Galla, B. M., Kaiser-Greenland, S., Locke, J., Ishijima, E., & Kasari, C. (2010). Effects of Mindful Awareness Practices on Executive Functions in Elementary School Children AU - Flook, Lisa. *Journal of Applied School Psychology*, 26(1), 70-95. doi:10.1080/15377900903379125
- Smith, R., Chernoff, M., Williams, P. L., Malee, K. M., Sirois, P. A., Kammerer, B., . . . Usitalo, A. (2012). Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *Pediatr Infect Dis J*, 31. doi:10.1097/INF.0b013e318253844b
- Sturdevant, C. B., Dow, A., Jabara, C. B., Joseph, S. B., Schnell, G., Takamune, N., . . . Swanstrom, R. (2012). Central Nervous System Compartmentalization of HIV-1 Subtype C Variants Early and Late in Infection in Young Children. *PLOS Pathogens*, 8(12), e1003094. doi:10.1371/journal.ppat.1003094
- Thorell, L. B., Lindqvist, S., Bergman Nutley, S., Bohlin, G., & Klingberg, T. (2009). Training and transfer effects of executive functions in preschool children. *Dev Sci*, 12(1), 106-113. doi:10.1111/j.1467-7687.2008.00745.x
- Tyor, W., Fritz-French, C., & Nath, A. (2013). Effect of HIV clade differences on the onset and severity of HIV-associated neurocognitive disorders. *J Neurovirol*, 19(6), 515-522. doi:10.1007/s13365-013-0206-6
- Uban, K. A., Herting, M. M., Williams, P. L., Ajmera, T., Gautam, P., Huo, Y., . . . Sowell, E. R. (2015). White matter microstructure among youth with perinatally acquired HIV is associated with disease severity. *Aids*, 29(9), 1035-1044. doi:10.1097/qad.0000000000000648
- Van Dalen, Y. W., Blokhuis, C., Cohen, S., Ter Stege, J. A., Teunissen, C. E., Kuhle, J., . . . Pajkrt, D. (2016). Neurometabolite alterations associated with cognitive performance in perinatally HIV-infected children. *Medicine (Baltimore)*, 95(12). doi:10.1097/MD.00000000000003093

801 Van den Hof, M., Ter Haar, A. M., Scherpbier, H. J., van der Lee, J. H., Reiss, P., Wit, F. W. N. M., . . . Pajkrt, D.
802 (2019). Neurocognitive development in perinatally HIV-infected adolescents on long-term treatment
803 compared to healthy matched controls: a longitudinal study. *Clinical Infectious Diseases*.
804 doi:10.1093/cid/ciz386

805 Walker, K. A., & Brown, G. G. (2018). HIV-associated executive dysfunction in the era of modern antiretroviral
806 therapy: A systematic review and meta-analysis. *J Clin Exp Neuropsychol*, 40(4), 357-376.
807 doi:10.1080/13803395.2017.1349879

808 Walker, S. Y., Pierre, R. B., Christie, C. D., & Chang, S. M. (2013). Neurocognitive function in HIV-positive children
809 in a developing country. *International Journal of Infectious Diseases*, 17(10), e862-867.
810 doi:10.1016/j.ijid.2013.02.014

811 Webb, L., Perry-Parrish, C., Ellen, J., & Sibinga, E. (2017). Mindfulness instruction for HIV-infected youth: a
812 randomized controlled trial. *AIDS Care*, 1-8. doi:10.1080/09540121.2017.1394434

813 Weber, V., Radeloff, D., Reimers, B., Salzmänn-Manrique, E., Bader, P., Schwabe, D., & Königs, C. (2017).
814 Neurocognitive development in HIV-positive children is correlated with plasma viral loads in early childhood.
815 *Medicine (Baltimore)*, 96(23), 6. doi:10.1097/md.00000000000006867

816 West, A. (2001). *Comparison of neuropsychological performances of asymptomatic HIV positive and HIV negative*
817 *adolescents and young adults (immune deficiency)*. (PhD in Psychology), Palo Alto University, ProQuest
818 database.

819 Willen, E. J., Cuadra, A., Arheart, K. L., Post, M. J. D., & Govind, V. (2017). Young adults perinatally infected with
820 HIV perform more poorly on measures of executive functioning and motor speed than ethnically matched
821 healthy controls. *AIDS Care*, 29(3), 387-393. doi:10.1080/09540121.2016.1234677

822 Williams, L. B., Geffken, G. R., Silverstein, J. H., & Storch, E. A. (2007). Type 1 Diabetes in Youth: The
823 Relationship Between Adherence and Executive Functioning. *Children's Health Care*, 36(2), 169-179.
824 doi:10.1080/02739610701335001

825 Yadav, S. K., Gupta, R. K., Hashem, S., Bhat, A. A., Garg, R. K., Venkatesh, V., . . . Haris, M. (2018). Changes in
826 resting-state functional brain activity are associated with waning cognitive functions in HIV-infected children.
827 *Neuroimage-Clinical*, 20, 1204-1210. doi:10.1016/j.nicl.2018.10.028

828 Zelazo, P. D., & Carlson, S. M. (2012). Hot and Cool Executive Function in Childhood and Adolescence:
829 Development and Plasticity. *Child Dev Perspect*, 6(4), 354-360. doi:10.1111/j.1750-8606.2012.00246.x

830 **Supplementary material**

831 Appendix 1.

832 Table I. Search strategy for PubMed

833 Table II. Downs and Black Quality Assessment Checklist

Table III. Application of Downs and Black Quality Assessment Checklist criteria according to study type

Table IV. Key data extracted into study database tables

Table V. Table of formulae used for conversions prior to meta-analysis

Appendix 2.

Table A. Characteristics of included observational studies: perinatally acquired HIV and perinatally HIV-exposed uninfected participants

Table B. Characteristics of included observational studies: behaviourally acquired HIV

Table C. Characteristics of included experimental and quasi-experimental studies

List of abbreviations

ART	antiretroviral therapy
BHIV	behaviourally acquired HIV
ADHD	attention deficit/hyperactivity disorder
CCR5	C-C chemokine receptor type 5
CDC C	Centres for Disease Control and Prevention Class C
CD4	cluster of differentiation 4
CCRT	computerised cognitive rehabilitation therapy
EF	executive function
HAND	HIV-associated neurocognitive disorder
HIV	human immunodeficiency virus
KABC-II	Kaufman Assessment Battery for Children, second edition
LMIC	low- and middle-income country
MBSR	mindfulness-based stress reduction therapy

PHIV	perinatal HIV infection
PHEU	perinatally HIV exposed uninfected
PHU	perinatally HIV-unexposed, uninfected
RCT	randomised controlled trial
SES	socio-economic status

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Tables

Table I. Study inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Population	<p>Three subpopulations of HIV-affected children and adolescents (2-24-years-old):</p> <ol style="list-style-type: none"> 1. Perinatally HIV exposed uninfected (PHEU): children whose mothers were HIV-positive during pregnancy and/or lactation but child was not infected; 2. Perinatal HIV infection (PHIV): children infected by their HIV-positive mothers during pregnancy and/or lactation; 3. Behaviourally acquired HIV (BHIV): HIV acquired by the child or adolescent later than the perinatal period by horizontal means, usually sexual or substance use behaviour. <p>HIV-positive participants were included regardless of ART status.</p>	<p>Transfusion-acquired HIV, animals</p>
Outcomes	<p>Primary:</p> <ol style="list-style-type: none"> 1. Core EFs (working memory, set-shifting, or inhibition) measured with objective cognitive task/s; 2. Complex EF (planning) measured with objective cognitive task/s; 3. Global EF in daily life measured with subjective behavioural report measures (e.g. self-report, parent-report). <p>Secondary:</p>	

-
1. measures of association between EF and other factors
(potential predictors or outcomes);
 2. change in EF from pre- to post-intervention (with or without comparison to change in a control arm).
-

Study design	1. Observational (cross-sectional or longitudinal), with or without controls	Case studies, case series, retrospective chart reviews.
	2. Experimental or quasi-experimental (pre-post) research studies	Systematic reviews, meta-analyses.
Source	Primary sources	Secondary sources (e.g.
	Grey literature (e.g. conference papers, theses)	reviews, editorials, textbooks, guidelines)

Key: ART = antiretroviral therapy; EF = executive function

Table II. Search strategy: sources and limits

Databases	Conferences	Search limits
MEDLINE, MEDLINE In Process & Other Non-Indexed Citations, CINAHL, PubMed, PsycINFO, Cochrane Database of Systematic Reviews, Web of Science, SCOPUS, WorldCat, EMBASE, EBSCO Child Development & Adolescent Studies, Global Index Medicus and OpenGrey.	International AIDS Conference (AIDS); IAS Conference on HIV Science; Conference on Retroviruses and Opportunistic Infections (CROI); International Conference on AIDS and STIs in Africa (ICASA); International Workshop on HIV Paediatrics; British HIV Association (BHIVA); European AIDS Conference; Australasian HIV & AIDS Conference.	<ol style="list-style-type: none"> human subjects published between January 1981 and January 2019 (updated: July 2019) any language (non-English full texts translated into English using Google Translate)

855 Table III. Potential predictors associated with executive function in children and adolescents with perinatally
 856 acquired HIV and/or perinatal HIV exposure without infection

Association and direction of effect on type of executive function			
Level	Significant in ≥ 1 study	Mixed findings	No association
Individual	Highest level of education (years of schooling): +WM, +PL (Brahmbhatt et al., 2017) Sleep duration: +WM (Foster et al., 2012)	Older age: +EF, -WM (Brahmbhatt et al., 2017; Martin et al., 2006; Rochat et al., 2016) Female sex: +WM (Maganlal, 2013), +TS (Maganlal, 2013), IC, PL, EF (Brahmbhatt et al., 2017; Martin et al., 2006; Rochat et al., 2016) Weight: +WM (Brahmbhatt et al., 2017), PL (Brahmbhatt et al., 2017), + PR EF (M. J. Boivin, Nakasujja, et al., 2017) Height: WM, PL (Brahmbhatt et al., 2017), +PR EF (M. J. Boivin, Nakasujja, et al., 2017) ADHD diagnosis: -PR EF, WM, IC, PL (Burkey et al., 2015)	
Perinatal			Low birth weight, duration of exclusive breastfeeding: EF (Rochat et al., 2016)
Caregiver	Biological parent as caregiver: +WM (Smith et al., 2012)	Maternal IQ: +WM (Smith et al., 2012), EF (Rochat et al., 2016)	Parental stress, perceived wealth,

		Caregiver depression: -PR EF (I. Familiar et al., 2018; I. Familiar et al., 2016), EF (Rochat et al., 2016)	maternal education (Rochat et al., 2016)
		Higher maternal age: +EF (Rochat et al., 2016)	
Family or household	Cash receipt, good parenting: +WM (Sherr et al., 2017)	Crèche attendance, mother as income provider, home stimulation: +EF (Rochat et al., 2016)	
		Higher socio-economic status: +WM (Smith et al., 2012), +TS (Patel et al., 2018), EF (Rochat et al., 2016)	
Treatment-related	Increase in age in those on ART: -WM, -PL (Brahmbhatt et al., 2017)	Currently on ART: +TS (Willen et al., 2017), -WM (Brahmbhatt et al., 2017)	
	Higher CD4% at ART initiation: +WM, +EF (Koekkoek et al., 2008)	Longer ART duration: ±WM (Brahmbhatt et al., 2017; Koekkoek et al., 2008; Martin et al., 2006; Nachman et al., 2012), ±IC (Koekkoek et al., 2008; Maganlal, 2013), +TS (Maganlal, 2013), PL (Brahmbhatt et al., 2017), EF (Martin et al., 2006)	
		NNRTI-based regimen: -WM (Nachman et al., 2012), EF (Bangirana, Boivin, Ruel, & Achan, 2015)	
		Delayed ART: -WM (Benki-Nugent et al., 2016), PL, TS (Benki-Nugent et al., 2016; Puthanakit et al., 2013; R. N. Robbins et al., 2019)	

Older age at ART initiation: -TS (Van den Hof et al., 2019), -WM (J. Hoare et al., 2019), EF, PL, SR EF, PR EF (Brahmbhatt et al., 2017; Kapetanovic et al., 2010; Nichols et al., 2015; Puthanakit et al., 2013)

HIV-related	<p>Past advanced disease (e.g. Stage 4 HIV or encephalopathy or more hospital admissions): -WM (R. N. Robbins et al., 2019; Smith et al., 2012; S. Y. Walker et al., 2013), -TS (R. N. Robbins et al., 2019), -EF (Judd et al., 2016; Malee et al., 2017), -SR & PR EF (Nichols et al., 2015)</p> <p>Current CD4 count: +IC (Malee et al., 2017; Ruel et al., 2012), +WM (Martin et al., 2006; Nachman et al., 2012; Ruel et al., 2012), EF (Nagarajan et al., 2012), PL(Ruel et al., 2012)</p> <p>Current viral load: -WM (Kapetanovic et al., 2010; Martin et al., 2006; Ruel et al., 2012), TS(R. N. Robbins et al., 2019), -IC (Malee et al., 2017; Ruel et al., 2012), -PL (Ruel et al., 2012), -PR EF (Nichols et al., 2015; Ruisenor-Escudero et al., 2015), EF (Bangirana et al., 2016; J. Hoare et al., 2019; Nagarajan et al., 2012)</p>	<p>Nadir CD4 count: TS (R. N. Robbins et al., 2019)</p>
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HIV-1 viral subtype A versus D: -WM, IC,
PL, EF (Bangirana et al., 2016; M. J. Boivin,
Ruel, et al., 2010)
Timing of disease severity: -EF, -SR EF
(Malee et al., 2017; Nichols et al., 2015)
Latent Toxoplasma infection: -EF (Ene et al.,
2016)

Key: + = positive; - = negative; \pm = positive or negative association; WM = working memory; PL = planning; EF= executive
function; PR = parent-reported; TS = task switching (set-shifting); IC = inhibitory control (inhibition); NNRTI = non-nucleoside
reverse transcriptase inhibitor; SR = self-reported; ART = antiretroviral therapy

Table IV. Potential markers associated with executive function in HIV-affected children and adolescents with perinatally acquired HIV and behaviourally acquired HIV

Association and directionality (if any)		
Level	Significant in ≥ 1 study	No association
Neuro-imaging	<p>PHIV:</p> <p>Higher Cho:Cre ratio in the brain: -WM, -EF (Van Dalen et al., 2016)</p> <p>Bilateral precentral gyrus, LH rostral middle frontal gyrus, and total GM volumes: +WM (Lewis-de los Angeles et al., 2017)</p> <p>Higher right IFO, EC, CP, SFO fractional anisotropy and axial diffusion on DTI: +WM (J. Hoare et al., 2019; Uban et al., 2015), +TS (J. Hoare et al., 2019)</p> <p>Abnormalities on CT-Brain: -WM (Martin et al., 2006)</p>	
Immuno-logical or vascular	<p>PHIV:</p> <p>Pro-inflammatory cytokine (TNF-α, IFN-γ) activation: -WM (Foster et al., 2012); hs-CRP: -TS, -EF, -WM (J. Hoare et al., 2019); LDL-C: +TS, +WM (J. Hoare et al., 2019); higher CSF NFH: -WM (Blokhuis et al., 2019)</p> <p>BHIV:</p> <p>Higher sCD14: -EF (Kim-Chang et al., 2019)</p> <p>Higher sVCAM-1: +WM, +EF (Kim-Chang et al., 2019)</p>	<p>PHIV:</p> <p>9 markers of vascular dysfunction: WM (Kapetanovic et al., 2010)</p>

Key: PHIV = perinatally acquired HIV infection; Cho = choline; Cre = creatine; WM = working memory; EF = executive function; LH = left hand side; GM = grey matter; IFO = inferior fronto-occipital fasciculus; EC = external capsule; CP = cerebral peduncle; SFO = superior fronto-occipital fasciculus; DTI = diffusion tensor imaging; CT = computed tomography; TNF = tumour necrosis factor; IFN = interferon; hs-CRP = high sensitivity C-reactive protein; TS = task switching; LDL-C = low-density

867 lipoprotein cholesterol; CSF = cerebrospinal fluid; NFH = neurofilament heavy-chain; BHIV = behaviourally acquired HIV;
868 sCD14 = soluble CD 14, a marker of macrophage activation; sVCAM = soluble vascular adhesion molecule, a marker of vascular
869 inflammation and endothelial activation; PHEU = perinatally HIV-exposed uninfected

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Table V. Potential functional outcomes associated with executive function in children and adolescents with perinatally acquired HIV and/or perinatally HIV-exposed without infection

Association and directionality (if any)			
Type of EF measure	Significant in ≥ 1 study	Mixed findings	No association
Cognitive tasks	+Academic achievement (Sirois et al., 2016)	+Adaptive behaviour (Sirois et al., 2016)	Adherence (Garcia-Navarro et al., 2013)
Behavioural report	+Education risk: WM problems (Nichols, Chernoff, et al., 2016; R. N. Robbins et al., 2019), TS problems (R. N. Robbins et al., 2019)	Adherence: + self-reported behavioural regulation; global self-report or caregiver-report EF (Garvie et al., 2017)	Medication responsibility (Garvie et al., 2017)

Key: EF = executive function; WM = working memory; TS = task switching (set-shifting)

Table VI. Potential predictors and outcomes associated with executive function in adolescents with behaviourally acquired HIV

Association and direction (if any) of effect on type of executive function			
Level	Significant in ≥ 1 study	Mixed findings	No association
Individual	Psychological distress: -EF (Nichols, Bethel, et al., 2016), -TS (Salama et al., 2013) Highest level of education: +TS (Salama et al., 2013)		Age, sex: TS (Salama et al., 2013)
HIV-related		Current CD4 count: +EF (Baker et al., 2014; Nichols, Bethel, et al., 2016), WM (Baker et al., 2014), TS (Salama et al., 2013) Current viral load: -EF (Baker et al., 2014; Nichols et al., 2013; Nichols, Bethel, et al., 2016), WM (Baker et al., 2014), TS (Salama et al., 2013)	Time since diagnosis: TS (Salama et al., 2013) Advanced disease: EF, WM (Baker et al., 2014)
Behavioural			Risky sexual & substance use behaviour (Baker et al., 2014)

Key: EF = executive function; TS = task switching (set-shifting); WM = working memory

Table VII: Summary of pooled effect size+ based on meta-analysis by subpopulations compared and type of executive function

Target group	Comparator group			
	PHU (not HIV-affected)	PHEU	Mixed PHEU/PHU (HIV-affected)	PHIV
PHIV	Verbal WM: -0.84 (-1.10, -0.58)* Visuospatial WM: -0.54 (-0.91, -0.18)* IC: -0.54 (-1.13, 0.04) TS: -0.33 (-0.89, 0.23) PL: -0.54 (-0.73, -0.36)* PR EF: 0.31 (-0.23, 0.85)	Verbal WM: -0.45 (-0.72, -0.18)* Visuospatial WM: -0.33 (-0.62, -0.04)* IC: -0.29 (-0.44, -0.15)* TS: -0.13 (-0.27, 0.01) PL: -0.21 (-0.49, -0.07) PR EF: 0.21 (-0.19, 0.60)	Verbal WM: -0.28 (-0.49, -0.07)* IC: -0.16 (-0.43, 0.10) TS: -0.28 (-0.53, -0.02)* SR EF: 0.43 (0.17, 0.68)*	CDC C vs non-C: Verbal WM: -0.34 (-0.60, -0.09)* IC: -0.43 (-0.73, -0.12)* TS: -0.30 (-0.50, -0.11)* PL: -0.17 (-0.63, 0.29)
PHIV slow progressors	Verbal WM: -0.21 (-0.55, 0.13) IC: -0.06 (-0.42, 0.30)			
PHEU	Verbal WM: -0.12 (-0.67, 0.42) Visuospatial WM: -0.12 (-0.40, 0.15)			

 IC: -0.20 (-1.62, 1.21)

PL: -0.09 (-0.67, 0.50)

PR EF: 0.10 (-0.08, 0.29)

 BHIV TS: -0.18 (-0.80, 0.44)

Key: [†]Effect sizes: Cohen's d with 95% confidence interval; PHU = perinatally HIV-unexposed uninfected; PHEU = perinatally HIV-exposed uninfected; PHIV = perinatally HIV-infected; WM = working memory; * = $p < 0.05$; IC = inhibitory control (inhibition); TS = task shifting (set-shifting); PL = planning; PR = parent-reported; EF = executive function; SR = self-reported; BHIV = behaviourally acquired HIV; vs = versus

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Figures

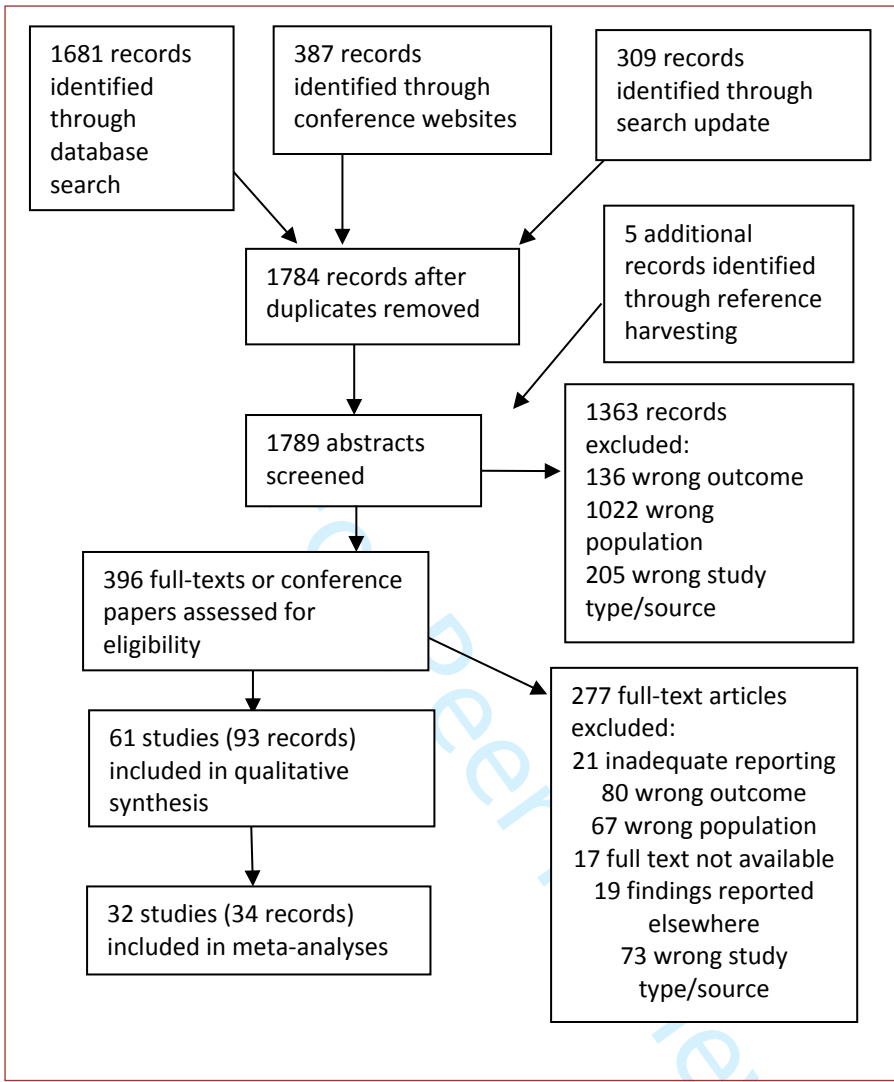
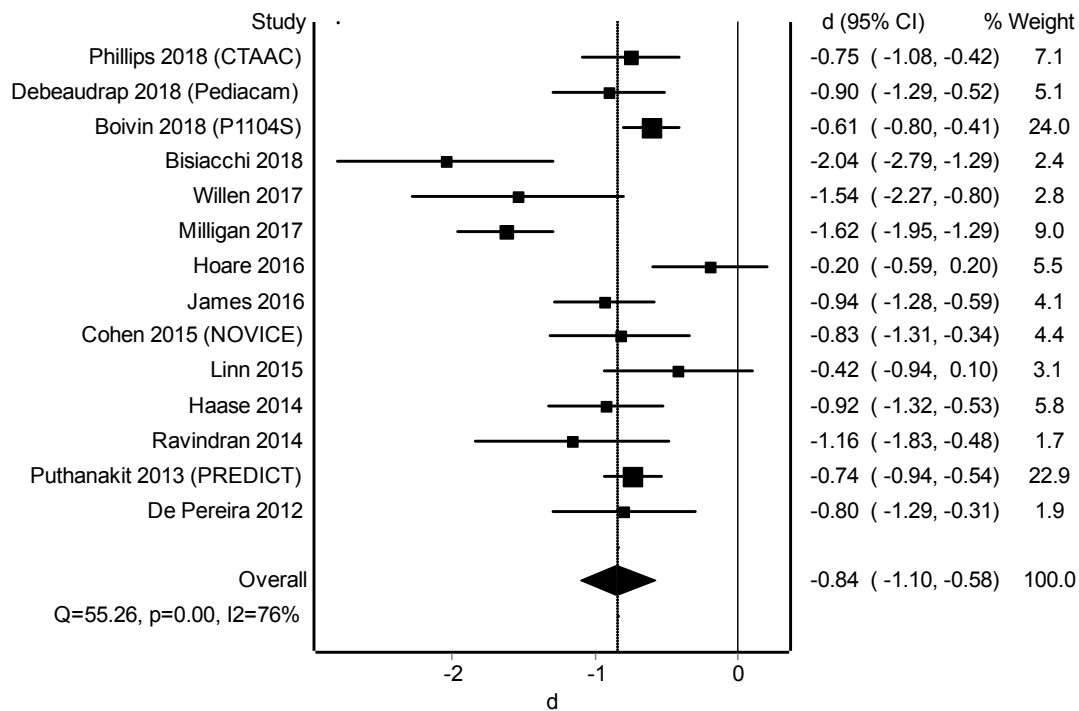
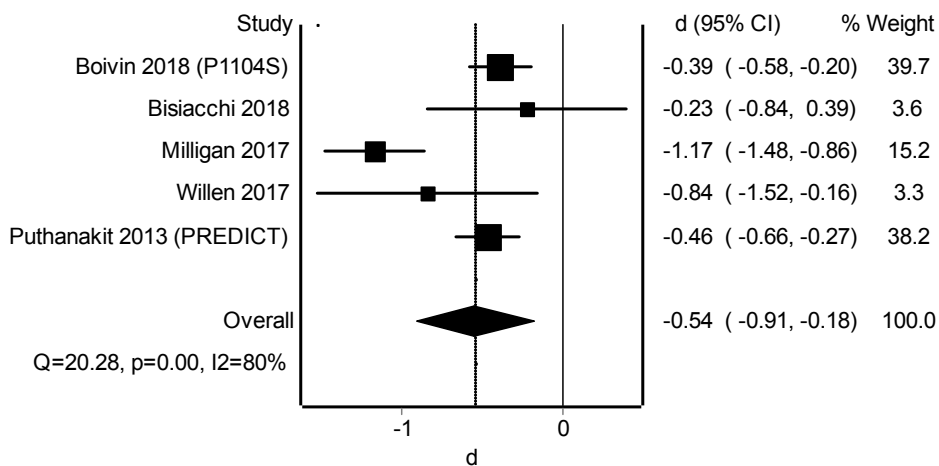


Figure 1: PRISMA flow diagram of study selection process

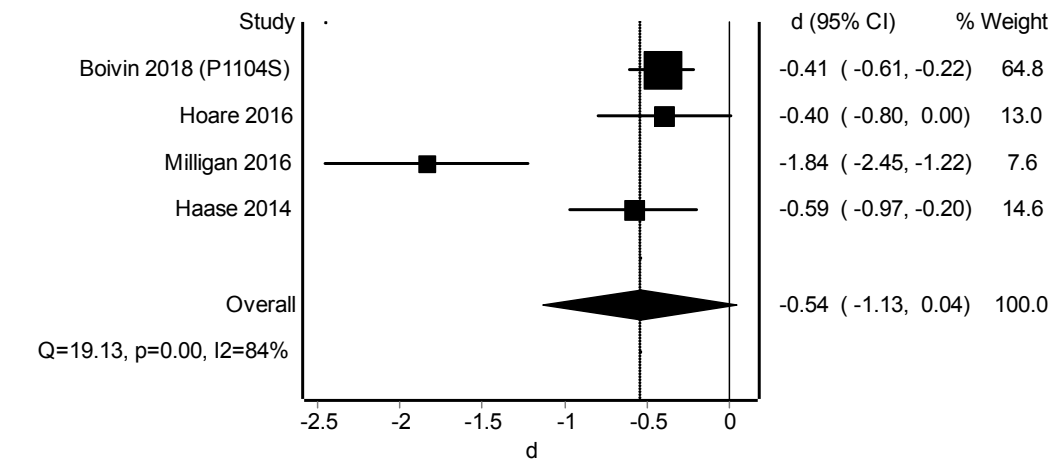
A: Verbal working memory



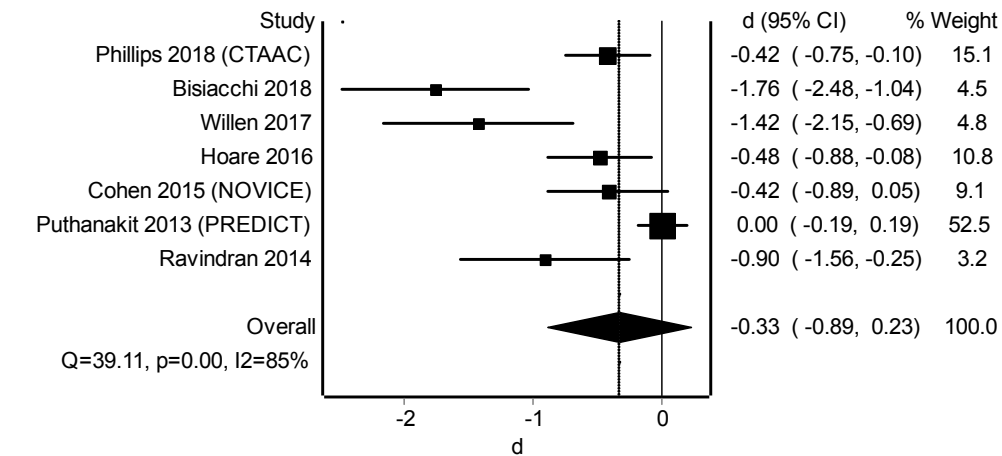
B: Visuospatial working memory



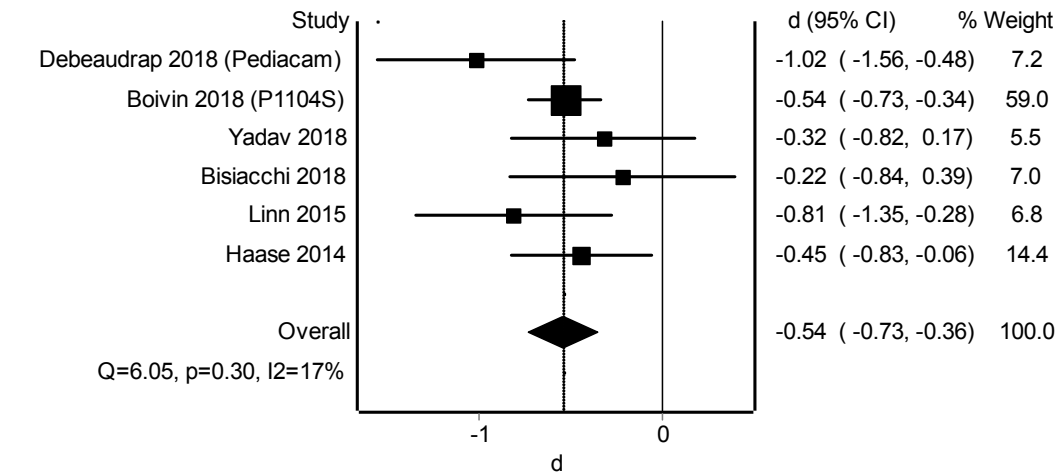
C: Inhibition



D: Set-shifting



E: Planning



F: Global executive function problems (caregiver-report)

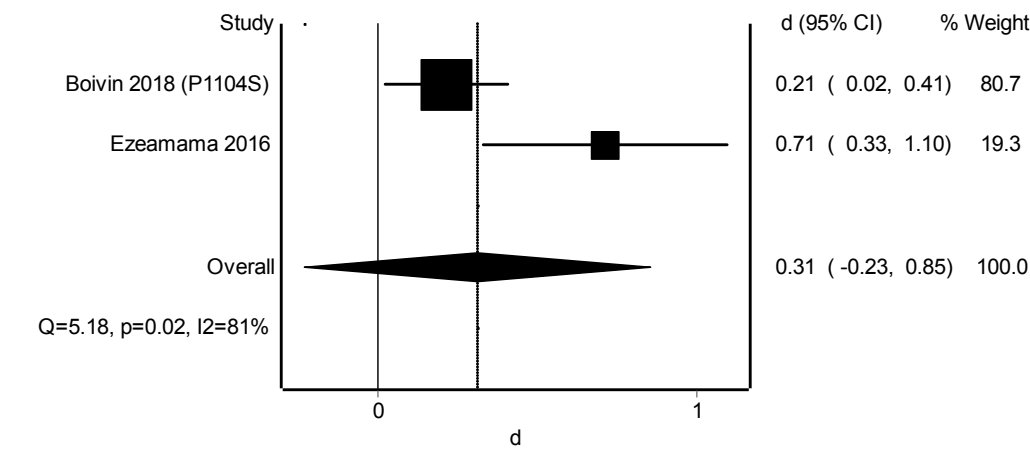
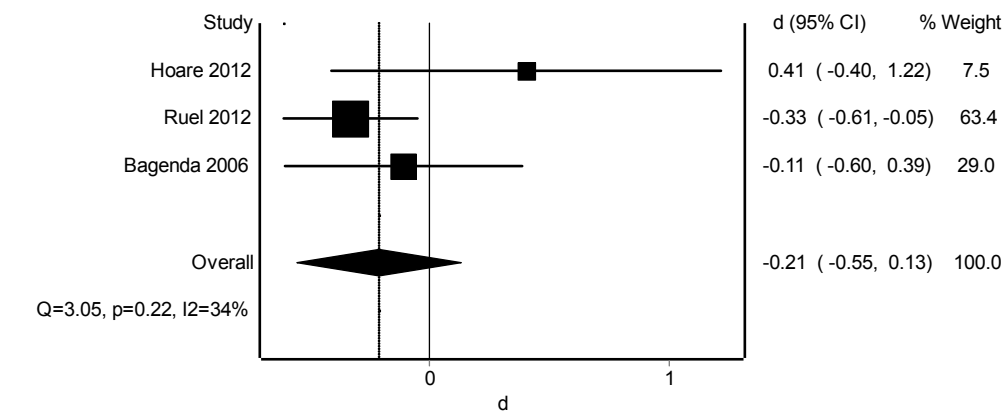


Figure 2: Forest plots of meta-analyses of effect size estimates in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. A-E: Negative effect sizes represent poorer performance by the HIV-positive group. F: Positive effect sizes represent more reported problems in the HIV-positive group.

A: Verbal working memory



B: Inhibition

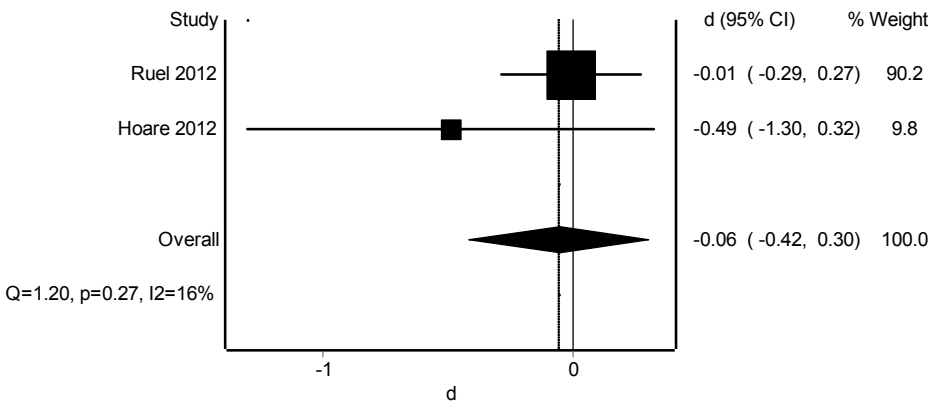
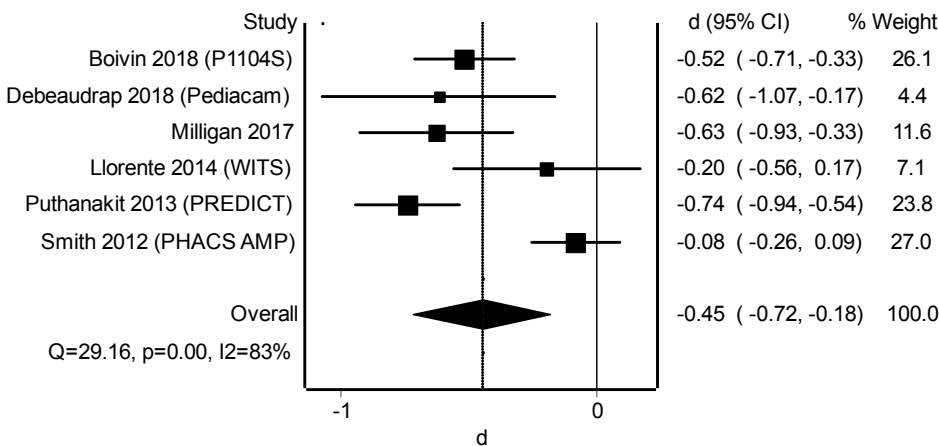
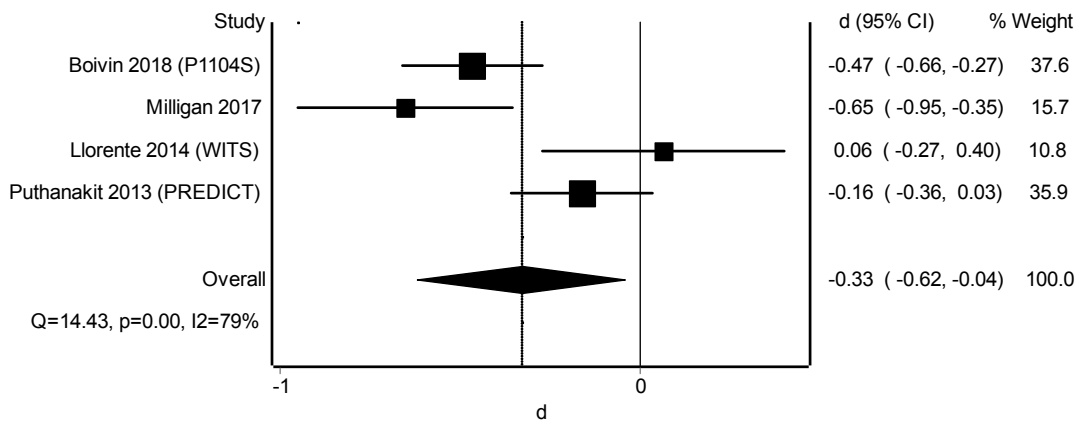


Figure 3: Forest plots of meta-analyses of effect size estimates in slow progressors with perinatally acquired HIV not on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

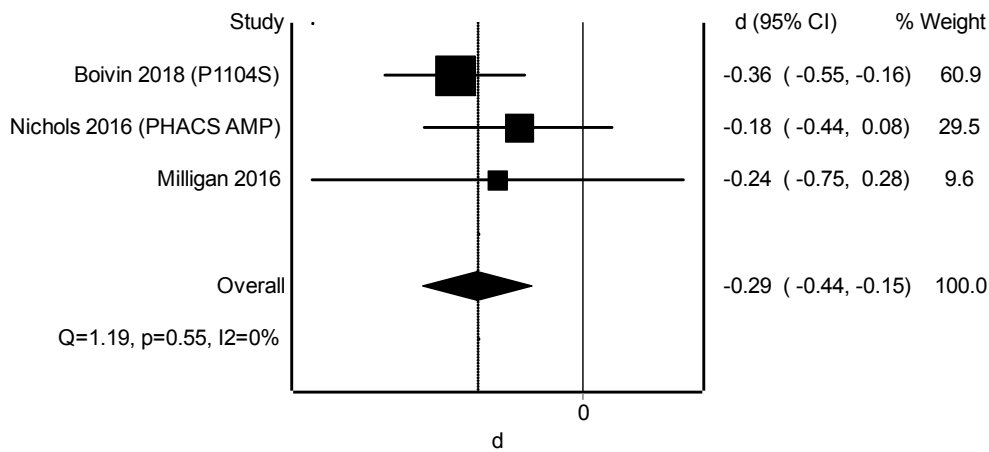
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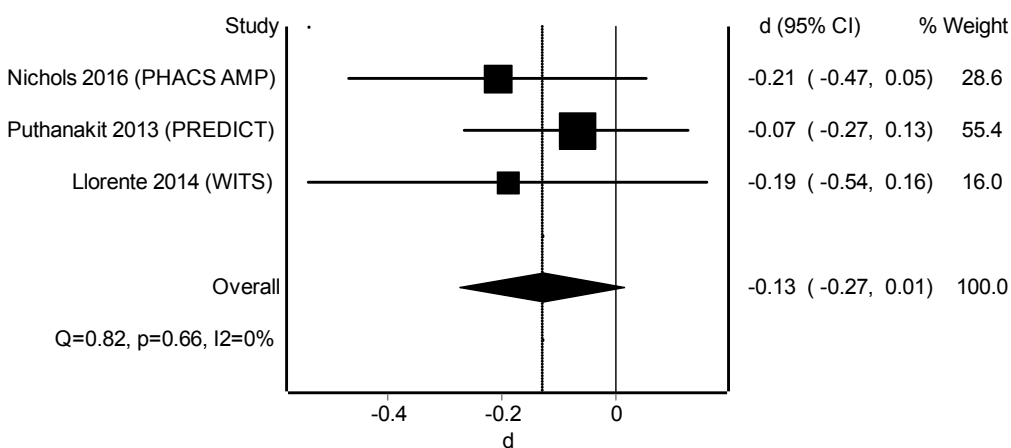
B: Visuospatial working memory



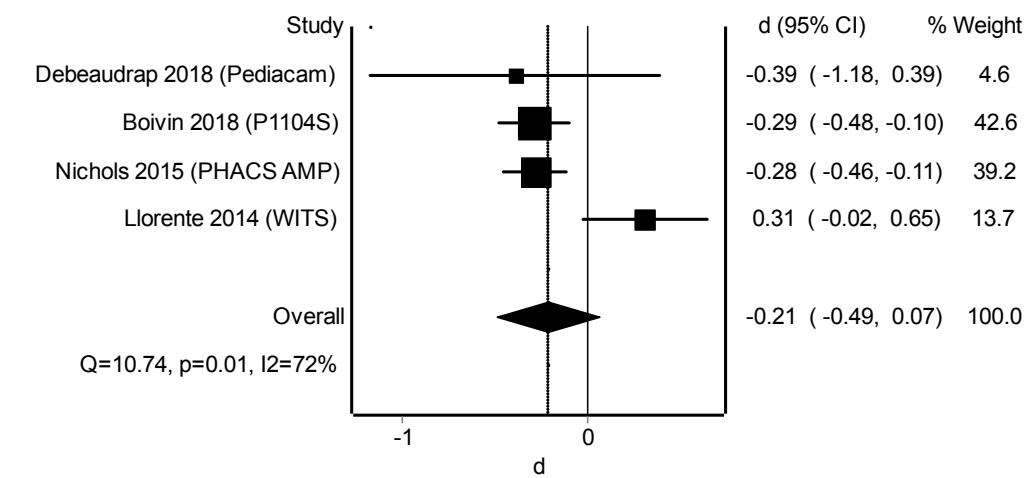
C: Inhibition



D: Set-shifting



E: Planning



F: Global executive function problems (caregiver-report)

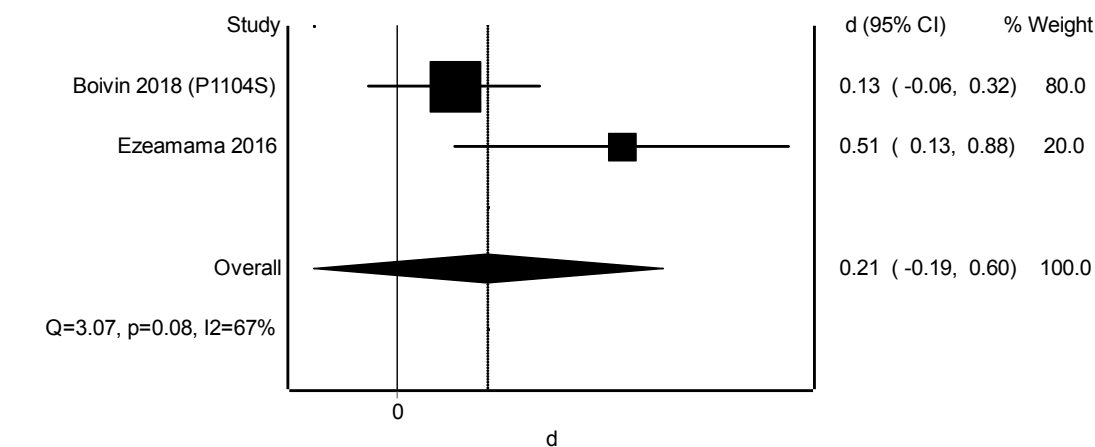
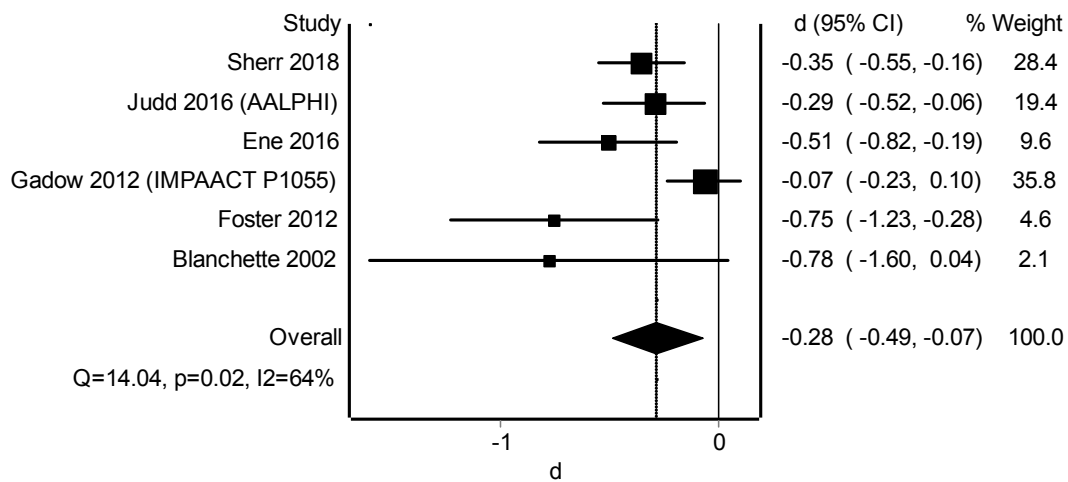
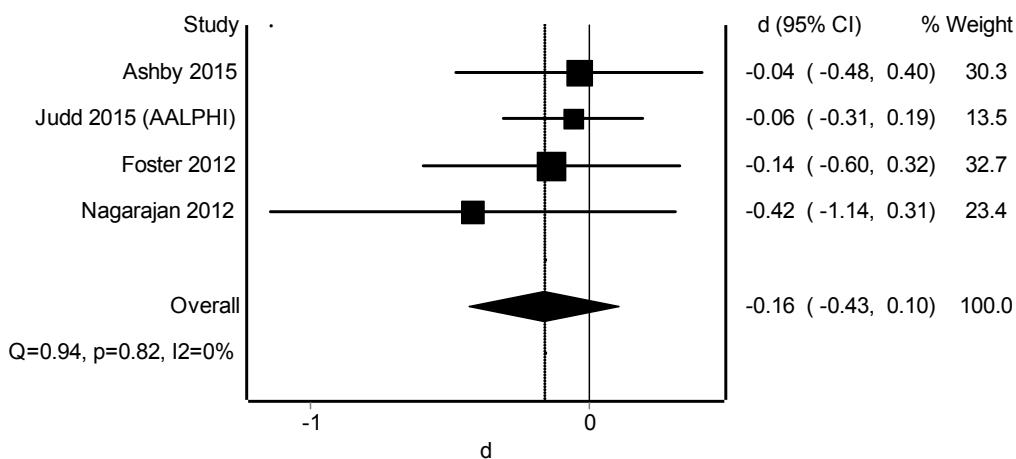


Figure 4: Forest plots of meta-analyses of effect size estimates in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. A-E: Negative effect sizes represent poorer performance by the HIV-positive group. F: Positive effect sizes represent more reported problems in the HIV-positive group.

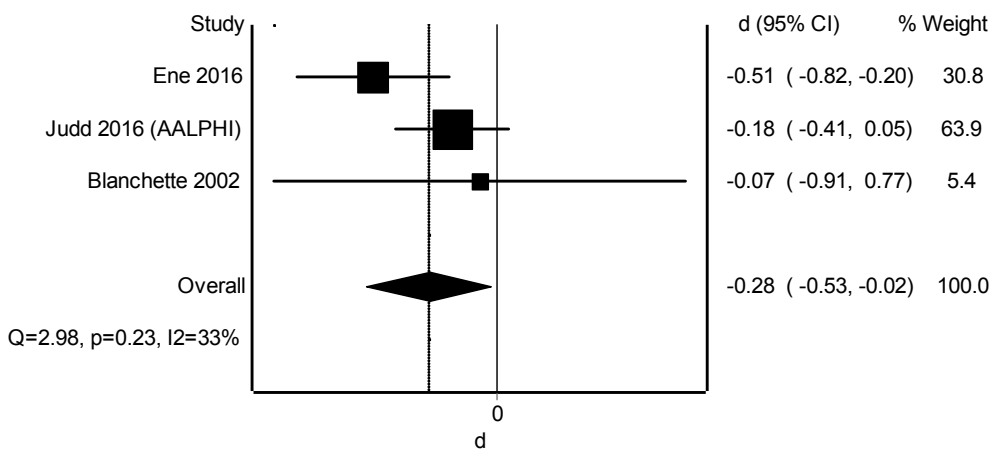
A: Verbal working memory



B: Inhibition



C: Set-shifting



D: Global executive function problems (self-report)

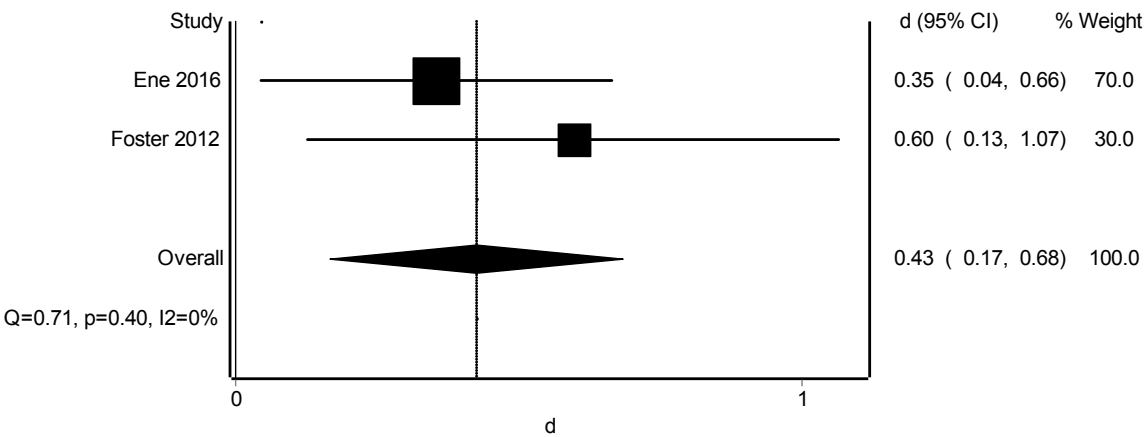
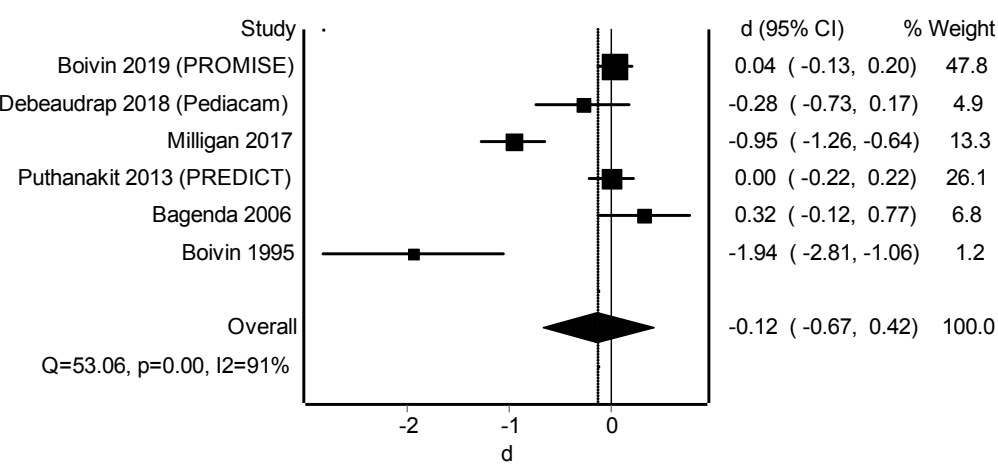
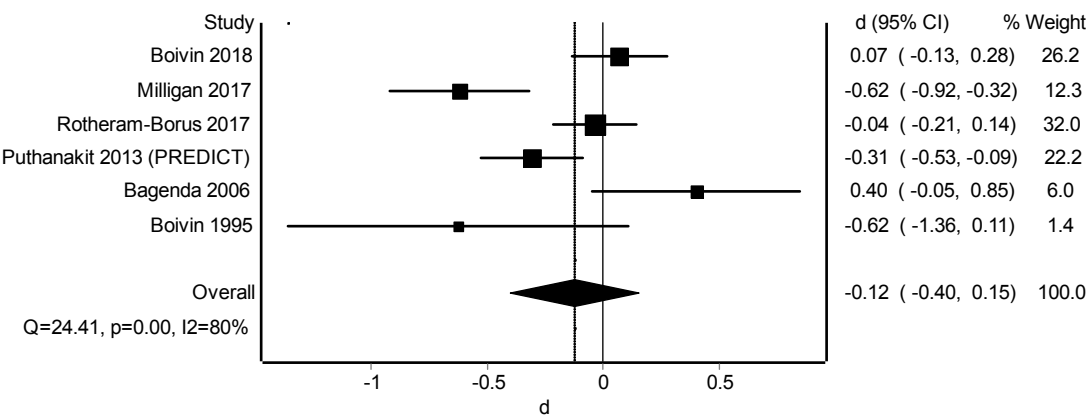


Figure 5: Forest plots of meta-analyses of effect size estimates in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to a mixed control group of perinatally HIV-exposed uninfected and perinatally HIV-unexposed uninfected children and adolescents. A-C: Negative effect sizes represent poorer performance by the HIV-positive group. D: Positive effect sizes represent more reported problems in the HIV-positive group.

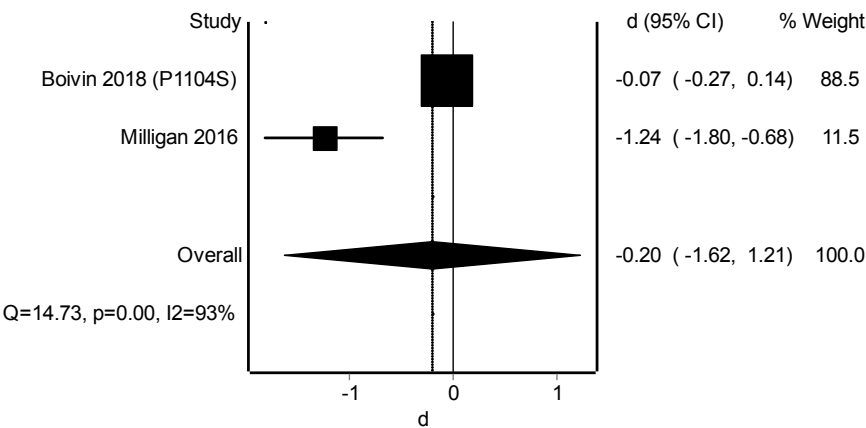
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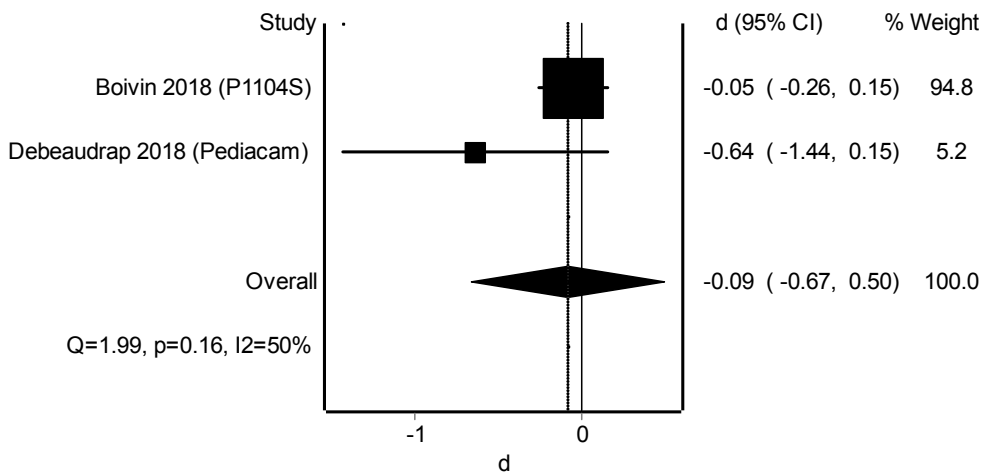
B: Visuospatial working memory



C: Inhibition



D: Planning



E: Global executive function problems (caregiver-report)

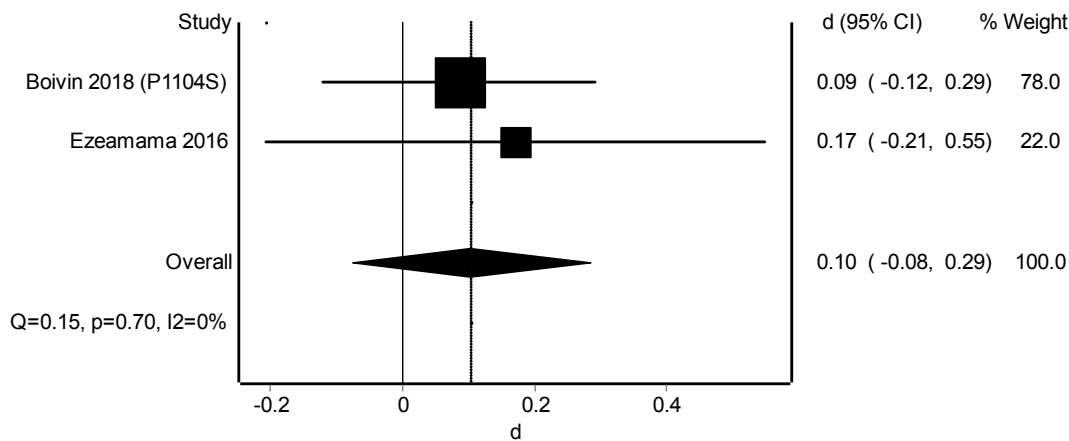
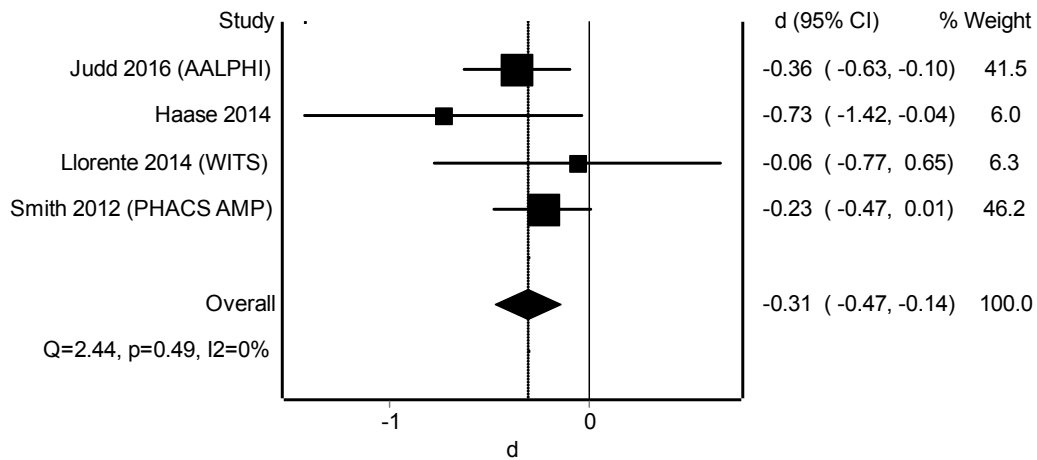
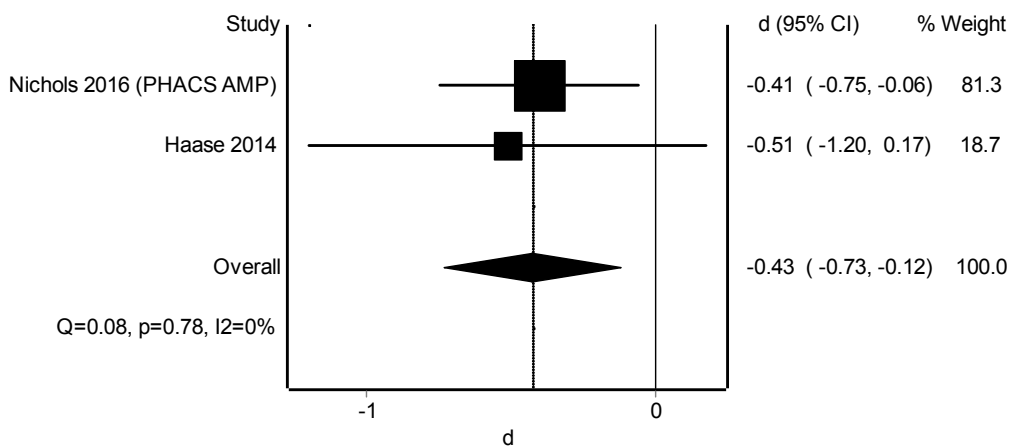


Figure 6: Forest plots of meta-analyses of effect size estimates in children and adolescents who are perinatally HIV-exposed uninfected compared to those who are perinatally HIV-unexposed uninfected. A-D: Negative effect sizes represent poorer performance by the HIV-exposed group. E: Positive effect sizes represent more reported problems in the HIV-exposed group.

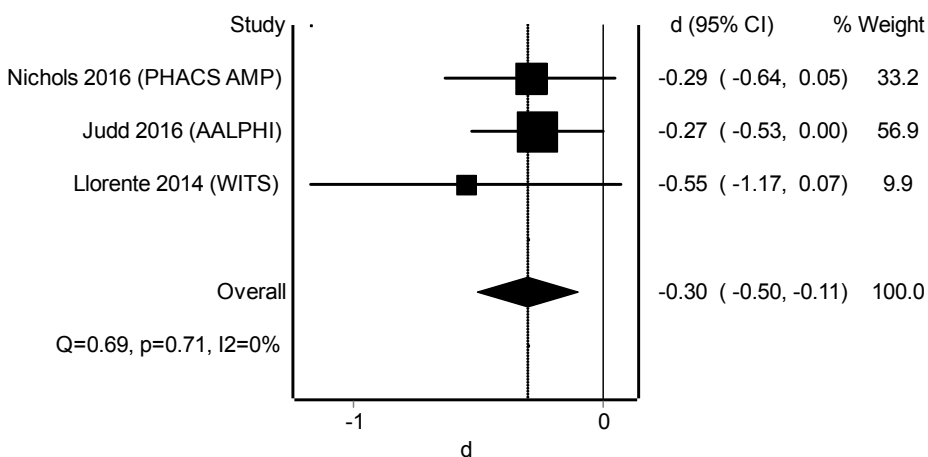
A: Verbal working memory



B: Inhibition



C: Set-shifting



D: Planning

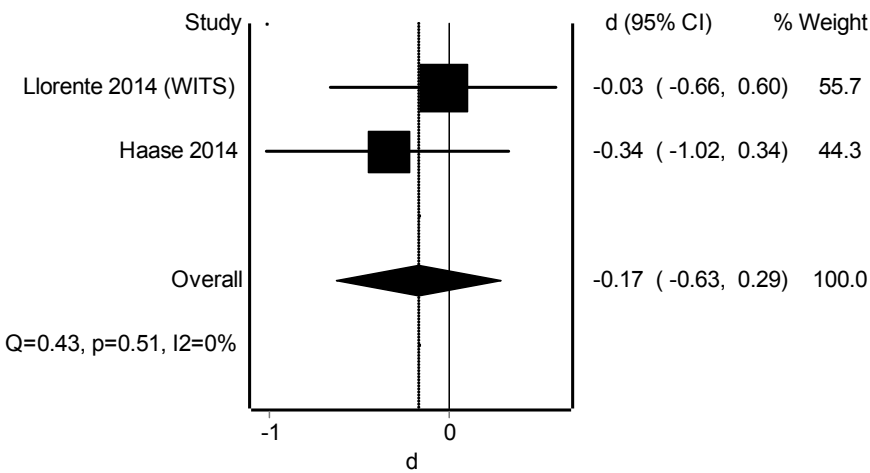


Figure 7: Forest plots of meta-analyses of effect size estimates in children and adolescents with perinatal HIV infection with a history of CDC Class C (more advanced) disease compared to those with non-C disease. Negative effect sizes represent poorer performance by the CDC Class C group.

Set-shifting

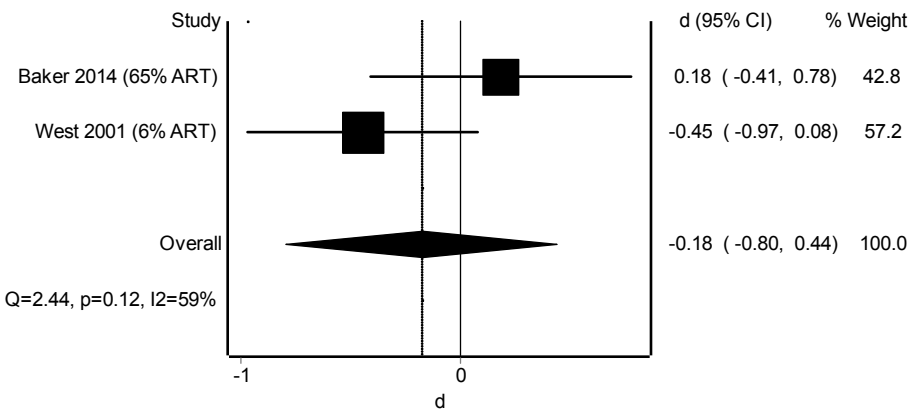


Figure 8: Forest plot of meta-analysis of effect size estimates in adolescents with behaviourally acquired HIV infection compared to HIV-negative controls. Negative effect sizes represent poorer performance by HIV-positive group.

Figure captions

Figure 1: PRISMA flow diagram of study selection process

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Figure 3: Forest plots of meta-analyses of effect size estimates in slow progressors with perinatally acquired HIV not on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

Figure 4: Forest plots of meta-analyses of effect size estimates in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. A-E: Negative effect sizes represent poorer performance by the HIV-positive group. F: Positive effect sizes represent more reported problems in the HIV-positive group.

Figure 5: Forest plots of meta-analyses of effect size estimates in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to a mixed control group of perinatally HIV-exposed uninfected and perinatally HIV-unexposed uninfected children and adolescents. A-C: Negative effect sizes represent poorer performance by the HIV-positive group. D: Positive effect sizes represent more reported problems in the HIV-positive group.

Figure 6: Forest plots of meta-analyses of effect size estimates in children and adolescents who are perinatally HIV-exposed uninfected compared to those who are perinatally HIV-unexposed uninfected. A-D: Negative effect sizes represent poorer performance by the HIV-exposed group. E: Positive effect sizes represent more reported problems in the HIV-exposed group.

Figure 7: Forest plots of meta-analyses of effect size estimates in children and adolescents with perinatal HIV infection with a history of CDC Class C (more advanced) disease compared to those with non-C disease. Negative effect sizes represent poorer performance by the CDC Class C group.

Figure 8: Forest plot of meta-analysis of effect size estimates in adolescents with behaviourally acquired HIV infection compared to HIV-negative controls. Negative effect sizes represent poorer performance by HIV-positive group.

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