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Developmental challenges in HIV infected children—An updated systematic review

Lorraine Sherr [a,*], Natasha Croome [a], Katherine Parra Castaneda [a], Katie Bradshaw [a], Rocio Herrero Romero [b]

[a] University College London (UCL), Department of Infection and Population Health, Royal Free Hospital, Rowland Hill Street, London, England NW3 2PF, UK
[b] Department of Social Policy and Intervention, University of Oxford, Barnett House, 32 Wellington Square, Oxford, England OX1 2ER, UK

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ABSTRACT

Children with HIV infection are at risk of developmental and behavioural challenges. A systematic review in 2009 set out the extent of delay documented in HIV positive children. This study presents an update and re-analysis. Full searches were conducted in Medline, Cochrane Database and PsycINFO, from which reviewers selected abstracts and followed references to provide detailed studies on HIV and cognitive performance in children under 18 to cover the period 2008–2013. The search generated 21 new studies, 17 of which (81%) report some form of cognitive delay for HIV positive children compared to controls. Some domains measured seem to be more affected than others, with mixed evidence on language and executive functioning. The need for more definitive control of variables was highlighted by the environmental factors contributing to behavioural and cognitive outcomes. In conclusion this systematic review confirms the prevalence of cognitive delay in children with HIV and explores the complexity of the issue. The findings suggest the need for internationally agreed monitoring tools and studies which control for known contributing factors. Research for children is needed with a full understanding of developmental challenges, to point the way forward for effective interventions.

Contents

* Corresponding author. Tel.: +44 207 830 2129.
E-mail addresses: l.sherr@ucl.ac.uk (L. Sherr), n.croome@ucl.ac.uk (N. Croome), k.parra@ucl.ac.uk (K. Parra Castaneda), k.bradshaw@ucl.ac.uk (K. Bradshaw), rocioherrero7@hotmail.com (R. Herrero Romero).

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1. Introduction

In adults there is growing understanding of the cognitive effects of HIV on functioning (Rackstraw, 2011). HIV can cross the blood brain barrier and permeate the central nervous system quite rapidly after exposure to the virus (Armstrong, 2006). Guidelines for assessment, diagnosis and treatment for HIV associated neurocognitive disorders (HAND) (Antinori et al., 2013) suggest it is appropriate to assess neurocognitive functioning in all patients with HIV, not just the symptomatic with regular follow up, specifically if there is evidence of deterioration or change in clinical status. There is still no definitive tool adapted and made appropriate for children. Cognitive challenge in adults refers to the loss of cognitive abilities. Cognitive challenge in children refers to the failure to gain cognitive abilities or to gain this at a different rate to comparison children. These are very different concepts.

It is of concern that less attention has been focused on children, as the effects on a developing infant may differ from a fully grown adult, and in order to plan for services, interventions, treatment and care, it is important to understand the cognitive abilities and developmental milestones of HIV positive children (Le Doaré, Bland, & Newell, 2012). There is a body of knowledge from the child development literature describing multiple factors contributing to cognitive development or developmental delay. Many of these factors can be found within families affected by HIV and AIDS. Children with HIV are subject to the potential impact of the virus, of antiretroviral treatment (ART) and environmental factors that are known to affect cognitive development. Reduced stimulation is a predictor of poor cognitive performance. In households where poverty and illness occur, parental responsiveness and environmental richness may be reduced. The documented risk factors for HIV infection in the first place are also often recorded as risks for cognitive or developmental delay. These include parental risks such as alcohol, drug use, diagnosed mental health disorders, chronic family illness and multiple stresses. HIV and AIDS clusters in families, and many of the burdens, such as stigma, illness, hospitalisation, bereavement, caretaker changes, separation and rejection are well documented as multiple shocks that such children face. Prematurity is also correlated with developmental delay, and it is well documented that HIV infection during pregnancy may elevate premature delivery rates (Townsend et al., 2010).

A systematic review in 2009 identified 54 studies cataloguing the cognitive effects of HIV in children (Sherr, Mueller, & Varrall, 2009). The review showed that studies were highly North American biased (66%) with European studies accounting for 13% and two from South America, two from South–east Asia and seven from Africa (13%), where the vast majority of HIV-infected children reside. The review showed a lack of comparability between studies as a wide array of different cognitive measures were used. Irrespective of measure used, 81% of studies reported a detrimental effect of HIV infection on neurocognitive development for HIV positive children compared to control groups, whilst three reported no differences and four had mixed findings. A more in depth understanding of various domains of cognitive functioning and how they are affected is

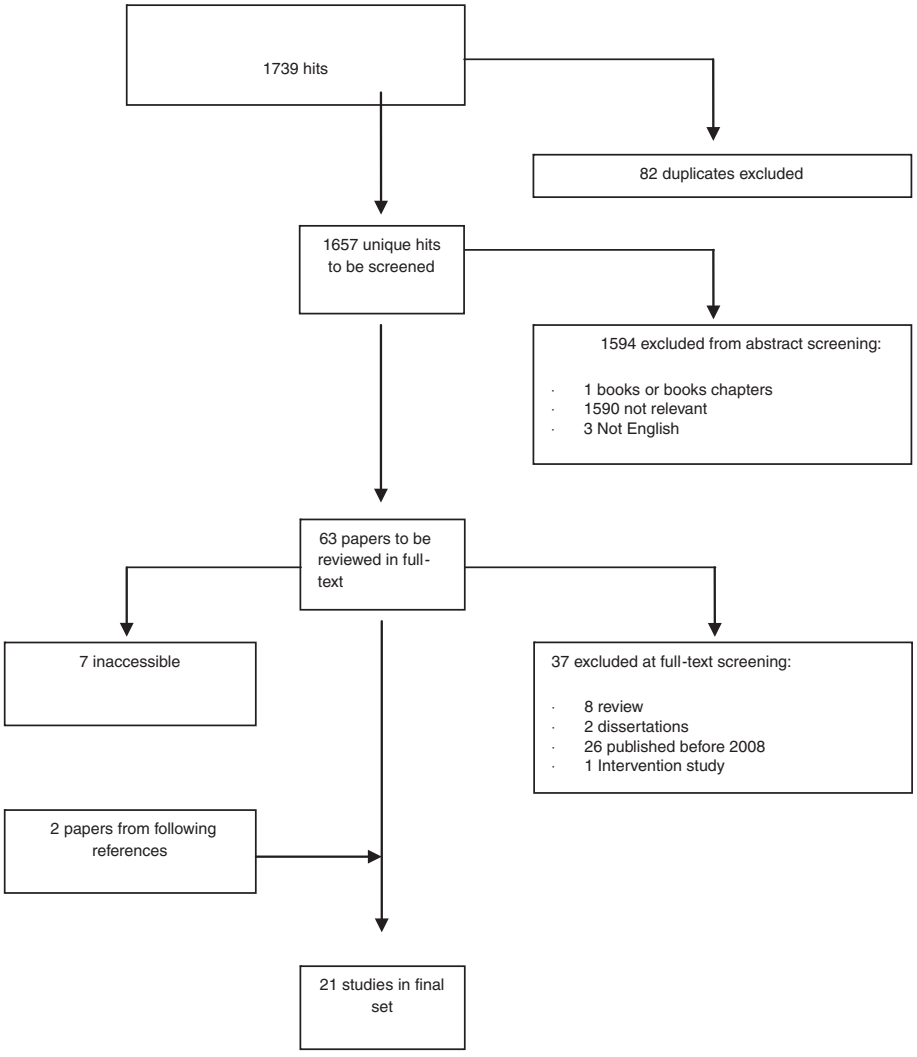

Fig. 1. Paper Inclusion Flowchart.

Table 1
Effects of HIV on performance.

Author	Study place	Sample size (N)	Formal measures	Domain measured	Gender	Cases and controls	HIV detrimental effect
Abubakar et al. (2009)	Kenya	367 aged 6–35 months	Kilifi Developmental Inventory (KDI)	Developmental	178 Males 169 Females	31 HIV+ 17 affected 319 control	Yes
Ananworanich et al. (2008)	Thailand	257 6–16 yrs	Child Behaviour Checklist (CBCL) (Thai Version)	Behavioural	52% Male 48% Female	66 HIV+ 64 hemat/oncologic 127 control	No
Baillieu and Potterton (2008)	South Africa	40 aged 18–30 months	Bayley Scale of Infant Development, 2nd Edition (BSID-II)	Developmental	N	40 HIV+	Yes
Baker et al. (2012)	USA	70 aged 8–14 yrs	The Children's Affective Representations of Relationships Scale (CARRS) Behaviour Assessment System for Children, Second Edition (BASC-2 SRP) Peabody Picture Vocabulary Test 3rd Ed (PPVT-III) The Friendship Quality Questionnaire (FQQ-R) The Friendship Interview	Behavioural Cognitive Social	39 Males 31 Females	21 HIV+ 24 affected 25 asthmatic	No
Brackis-Cott et al. (2009)	USA	325 aged 9–16 yrs	Peabody Picture Vocabulary Test Third Edition (PPVT-III) Reading Subtest of the Wide Range Achievement Test Third Edition (WRAT-3)	Cognitive	161 Males 164 Females	196 HIV+ 129 control	Yes
Chernoff et al. (2009)	USA	575 aged 6–17 yrs	Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) The Child and Adolescent Symptom Inventory-4R (CASI-4R) The Youth's (Self-Report) Inventory (YI-4) The Child (Self-Report) Inventory-4 (CSI-4)	Behavioural Cognitive Mood	285 Males 290 Females	319 HIV+ 256 affected	Yes (mixed)
Dobrova-Krol et al. (2010)	Ukraine	61 mean age 50.9 months	Snijders–Oomen Nonverbal Intelligence Test (SON-R) Emotional Availability Scales (EAS) Strange Situation Procedure (SSP)	Cognitive Social	32 Males 32 Females	29 HIV 35 control	No
Ferguson and Jelsma (2009)	South Africa	86 aged 1–33 months	Bayley Scales of Infant Development 2nd Edition (BSID-II)	Developmental	N	51 HIV+ 35 control	Yes
Gadow et al. (2010)	USA and Puerto Rico	575 aged 6–17 yrs	Child and Adolescent Symptom Inventory-4R (CASI-4R) Youth's (Self-Report) Inventory-4R (YI-4R) Child (Self-Report) Inventory-4 (CSI-4) Social and Academic Functioning Questionnaire Wechsler Intelligence Scale for Children-IV (WISC-IV)	Behavioural Cognitive Mood Social	285 Males, 297 Females	323 HIV+ 259 control	Yes (mixed)
Gadow et al. (2012)	USA	278 aged 6–17 yrs	Child and Adolescent Symptom Inventory (CASI-4R) Youth Self-Report inventory (YI-4) Child Self-Report inventory (CSI-4) Wechsler Intelligence Scale (WISC-IV)	Behavioural Cognitive Mood	48% Males 52% Female	296 HIV+ 229 affected	Yes

Isaranurug and Chompikul (2009)	Thailand	388 aged 6–12 yrs	Standardised Test for Thai Children	Cognitive	50.3% Male 49.7% Female	74 HIV+ 223 control 91 unknown HIV status	Yes (mixed)
Jelsma et al. (2011)	South Africa	44 aged 35–74 months	Peabody Developmental Motor Scale (PDMS-II)	Cognitive Developmental	24 Males 20 Females	23 HIV+ 21 control	Yes
Koekkoek et al. (2008)	Netherlands	22 medium age 9.46 yrs	Revised version of Snijders-Oomen Nonverbal Intelligence Test (SON-R) Global Intelligence Test Amsterdam's Neuropsychological Tasks Program tests (ANT) Verbal Fluency Task	Cognitive	11 Males 11 Females	22 HIV+	Yes
Lowick et al. (2012)	South Africa	60 aged 5–6 yrs	Griffiths Mental Development Scales-Extended Revised Version (GMDS-ER)	Developmental	30 Males 30 Females	30 HIV+ 30 control	Yes
Maleea et al. (2011)	USA and Puerto Rico	416 aged 7–16 yrs	Behaviour Assessment System for Children, 2nd edition (BASC-2)	Behavioural	199 Males 217 Females	295 HIV+ 121 affected	Yes (mixed)
Mellins et al. (2009)	USA	325 aged 9–16 yrs	Diagnostic Interview Schedule for Children (DISC-IV)	Behavioural Mood	166 Males 174 Females	196 HIV+ 129 control	Yes (mixed)
Rice et al. (2012)	USA and Puerto Rico	437 aged 7–16 yrs	Clinical Evaluation of Language Functioning-Fourth Edition (CELF-4)	Cognitive	221 Males, 216 Females	284 HIV+ 153 affected	No
Serchuck et al. (2010)	USA & Puerto Rico	576 aged 6–17 yrs	Wong Baker FACES Short-Form McGill Pain Questionnaire (SF-MPQ) Symptom Inventory (SI-4)	Cognitive	285 Males 291 Females	320 HIV+ 256 affected/control	Yes (mixed)
Thomaidis et al. (2010)	Greece	60 aged 3–18 yrs	The Wechsler Intelligence Scale III (WSCI-III) Griffiths Mental Abilities Scales (GMDS-ER) Strengths and Difficulties Questionnaire (SDQ) CT/MRI scan	Behavioural Cognitive	24 Males 36 Females	20 HIV+ 40 control	Yes
Van Rie et al. (2008)	Democratic Republic of Congo	160 aged 18–72 months	Bayley Scales of Infant Development 2nd Edition (BSID-II) Peabody Motor Scales (PDMS-II) Snijders-Oomen Nonverbal Intelligence (SON) Rossetti Infant-Toddler Language Scale (RITLS)	Cognitive Developmental	80 Males 80 Females	35 HIV+ 35 affected 90 control	Yes
Van Rie et al. (2009)	Democratic Republic of Congo	160 aged 18–71 months	Bayley Scales of Infant Development 2nd Edition (BSID-II) Peabody Developmental Motor Scales (2nd Edition) (PDMS-II) Snijders-Oomen Nonverbal Intelligence Test (SON)	Cognitive Developmental	80 Males 80 Females	35 HIV+ 35 affected 90 control	Yes

Table 2
Effects of HIV reported in studies.

Study	Sample	Cognitive measure	Score HIV	Score HIV affected	Score control	Score Other	P value (HIV + to controls)
Abubakar et al. (2009) Kenya	367 children 6–35 months (31, HIV+, 17 affected, 319 control)	KDI Psychomotor	M = 0.08, SD = 0.84	M = 0.11, SD = 0.60	M = −0.91, SD = 1.86		.05
		Locomotor	M = 0.06, SD = 0.84	M = 0.27, SD = 0.65	M = −0.76, SD = 1.98		ns
		Eye-hand co-ordination	M = 0.09, SD = 0.90	M = -0.10, SD = 0.65	M = −0.90, SD = 1.50		.05
Ananworanich et al. (2008) Thailand	257 children 6–16 yrs (66 HIV+, 127 control, 64 hematologic/oncologic diseases)	CBCL					ns
Baillieu and Potterton (2008) South Africa	40 children 18–30 months (All HIV+)	*BSID (Mental)*	70%	Chronological Age Comparison			<.001
		Sig delayed					
		Mildly delayed	20%				
		Normal	10%				
		BSID (Motor) Sig delayed	77.5%				<.001
		Mildly delayed	10%				
		Normal	10%				
		Accelerated	2.5%				
		Gross Motor Delay	85%				<.001
		Fine Motor Delay	12.5%				
		Global Language Delay	82.5%				
Baker et al. (2012) USA	70 children 8–14 yrs (21 HIV+, 24 affected, 25 asthmatic)	*CARRS* Affect Tone	M = 53.62, SD = 8.46	M = 56.75, SD = 8.96		M = 50.64, SD = 9.11	ns (HIV + & affected)
		Emotional Investment	M = 52.14, SD = 4.61	M = 53.88, SD = 5.91		M = 47.92, SD 9.08	
		BASC-2 SRP	M = 50.62,	M = 50.29,		M = 47.08,	
		Interpersonal Relations	SD = 9.3	SD = 11.73		SD = 11.17	
		Peabody Picture Vocab	M = 92.0, SD = 12.15	M = 92.67, SD = 8.3		M = 92.16, SD = 10.66	
		FQQ-R	M = 0.5,	M = 0.54,		M = 0.38,	
		Companionship & Recreation	SD = 0.15	SD = 0.16		SD = 0.19	
		Validation & Caring	M = 3.18, SD = 0.48	M = 3.45, SD = 0.54		M = 2.83, SD = 0.95	
		Help & Guidance	M = 2.78, SD = 0.72	M = 2.94, SD = 0.56		M = 2.55, SD = 0.82	
		Intimate Disclosure	M = 2.09, SD = 0.96	M = 2.85, SD = 0.75		M = 2.17, SD = 1.04	
		Conflict Resolution	M = 2.70, SD = 0.97	M = 3.14, SD = 0.74		M = 2.60, SD = 1.01	
		Conflict & Betrayal	M = 1.08, SD = 0.63	M = 0.82, SD = 0.61		M = 1.05, SD = 0.69	
Brackis-Cott et al. (2009) USA	325 children 9–16 yrs (196 HIV+, 129 control)	PPVT-III	83.82 (SD = 14.81)		87.55 (SD = 13.47)		<.05
		WRAT-3 Reading	88.23 (SD = 17.92)		93.77 (SD = 17.72		<.05
Chernoff et al. (2009) USA	575 children 6–17 yrs (319 HIV+, 256 affected)	CASI-4R & DSM-IV *Screening Prevalence*	194(61%)		115(61%)		ns
		Any problems					
		ADHD	56(18%)		42(17%)		ns
		Aggression	45(14%)		41(16%)		ns
		Mood	55(17%)		51(20%)		ns
		Anxiety	119(37%)		111(44%)		ns
		Impairment	46(15%)		35(14%)		ns
		Any problems					
		ADHD	38(12%)		28(11%)		ns
		Aggression	19(6%)		17(7%)		ns
		Mood	4(1%)		7(3%)		ns
		Anxiety	17(5%)		12(5%)		ns
		Impairment & Screening	55(17%)		42(17%)		ns
		Any problems					
		ADHD	37(12%)		28(11%)		ns
		Aggression	20(6%)		19(8%)		ns
		Mood	9(3%)		11(4%)		ns
		Anxiety	9(3%)		11(4%)		ns
Dobrova-Krol et al. (2010) Ukraine	61 children, mean age 50.9 months (29 HIV+, 32 control)	SON-R	M = 78.00, SD = 16.87		M = 97.63, SD = 19.40		<.05
		Family reared children					
		Institution children	M = 64.00, SD = 14.32		M = 67.31, SD = 18.97		ns
		EAS	M = −.19,		M = 1.39,		<.05
		Family reared children	SD = 1.34		SD = 1.43		
		Institution children	M = −0.62, SD = 1.41		M = −0.96, SD = 1.62		ns

Table 2 (*continued*)

Study	Sample	Cognitive measure	Score HIV	Score HIV affected	Score control	Score Other	P value (HIV + to controls)
		SSP	M = 4.63,		M = 5.97,		<.05
		Attachment Security	SD = 1.31		SD = 1.74		
		Family reared children					
		Institution children	M = 4.27,		M = 3.75,		ns
			SD = 1.87		SD = 1.94		
		Attachment	M = 4.14,		M = 2.79,		ns
		Disorganisation	SD = 2.30		SD = 1.66		
		Family reared children					
		Institution children	M = 4.00,		M = 4.44,		ns
			SD = 2.34		SD = 1.88		
Ferguson and Jelsma (2009) South Africa	86 age 1–33 mths (51 HIV+, 35 control)	*BSID (Motor)*	9.8%		65.7%		<.001
		Normal					
		Mildly delayed	23.5%		28.6%		
		Significantly delayed	66.6%		5.7%		
Gadow et al. (2010) USA & Puerto Rico	575 children 6–17 yrs (319 HIV+, 256 control)	CASI-4R	47 (24%)		35 (33%)		ns
		Any disorder					
		ADHD	20 (10%)		18 (17%)		ns
		Oppositional defiant	17 (9%)		10 (10%)		ns
		Conduct disorder	1 (1%)		9 (9%)		<.001
		Generalised anxiety	19 (10%)		13 (12%)		ns
		Separation Anxiety	8 (4%)		5 (5%)		ns
		Depression	13 (7%)		11 (10%)		ns
		Manic episode	8 (4%)		9 (9%)		ns
		Caregiver Reported	M = 1.9,		M = 1.9, SD = 1.5		ns
		Social Functioning	SD = 1.4				
		Academic Functioning	M = 2.7,		M = 2.0, SD = 2.1		<.001
			SD = 2.2				
		WISC-IV	M = 8.5,		M = 8.9, SD = 3.0		ns
		Working Memory subtest	SD = 3.2				
		Processing Speed subtest	M = 8.0,		M = 9.4, SD = 3.1		<.001
			SD = 3.1				
Gadow et al. (2012) USA & Puerto Rico	278 children 6–17 yrs (157 HIV+, 121 affected)	CASI-4R	69%		70%		ns
		Any symptom					
		Screening cut-off					
		Clinical cut-off	24%		25%		
		Impairment cut-off	23%		20%		
		ADHD	25%		26%		ns
		Screening cut-off					
		Clinical cut-off	16%		15%		
		Impairment cut-off	16%		10%		
		Disruptive Behaviours	22%		21%		ns
		Screening cut-off					
		Clinical cut-off	12%		14%		
		Impairment cut-off	11%		13%		
		Depression	21%		30%		ns
		Screening cut-off					
		Clinical cut-off	6%		10%		
		Impairment cut-off	4%		5%		
		Anxiety	24%		37%		ns
		Screening cut-off					
		Clinical cut-off	11%		10%		
		Impairment cut-off	4%		7%		
		Wechsler Intelligence Scale	M = 8.6,		M = 8.8, SD = 3.0		ns
		Working memory	SD = 3.1				
		Processing Speed	M = 8.1,		M = 9.4, SD = 3.0		<.001
			SD = 3.0				
Isaranurug and Chompikul (2009) Thailand	388 children 6–12 yrs (74 HIV+, 223 control, 91 unknown HIV status)	Standardised Test for Thai Children	61.0 (10.3)		61.8 (8.9)	62.0 (8.8)	ns
		Moral Character					
		Self-control	17.7 (3.4)		18.8 (3.0)	18.1 (3.1)	<.05
		Sensitive to others	23.7 (5.3)		23.8 (4.7)	24.3 (4.6)	ns
		Acceptance of criticism	19.6 (4.0)		19.3 (3.7)	19.6 (3.7)	ns
		Ability	48.5 (7.5)		50.2 (7.3)	49.9 (7.9)	ns
		Effort	18.3 (3.8)		19.1 (3.7)	19.0 (3.7)	ns
		Well Adaptation	14.4 (3.0)		14.8 (3.0)	14.8 (3.3)	ns
		Expressiveness	15.8 (4.5)		16.3 (3.2)	16.1 (3.0)	ns
		Contentment	49.7 (8.1)		50.1 (9.5)	51.0 (7.8)	ns
		Self-esteem	15.7 (3.4)		16.0 (3.4)	16.7 (2.9)	ns
		Quick Recovery	15.7 (3.2)		17.0 (3.2)	16.6 (3.3)	<.05
		Cheerfulness	18.3 (4.2)		17.0 (5.8)	17.8 (3.8)	ns
		Overall	159.1 (21.4)		162.1 (21.5)	163.0 (21.4)	ns
Jelsma et al. (2011) South Africa	44 children 35–74 months (23 HIV, 21 control)	PDMS-II	M = 83.8,		M = 96.6,		<.001
		Fine Motor Quotient	SD = 13.2		SD = 13.8		
		Gross Motor Quotient	M = 77.9,		M = 96.1,		<.001
			SD = 11.5		SD = 11.5		

(*continued on next page*)

Table 2 (*continued*)

Study	Sample	Cognitive measure	Score HIV	Score HIV affected	Score control	Score Other	P value (HIV + to controls)
		Total Motor Quotient	M = 79.3, SD = 10.2		M = 95.3, SD = 11.8		<.001
Koekkoek et al. (2008) Amsterdam	22 children medium age 9.46 yrs (All HIV+)	SON-R	M = 95.0, SD = 16.2				ns
		Global Intelligence Test	M = −0.78, SD = 0.83				<.01
		Pattern Recognition Speed Accuracy	M = −0.49, SD = 0.88				<.05
		Tracking Accuracy	M = −0.27, SD = 1.28				ns
		Tapping	M = 0–0.48, SD = 1.47				ns
		ANT Pursuit Accuracy	M = −0.18, SD = 1.18				ns
		Shifting Set—Speeds 1 & 2	M = −0.83, SD = 1.13				<.01
		Speed (part 3)	M = −1.69, SD = 1.16				<.01
		Accuracy 1 & 2)	M = −0.59, SD = 1.16				<.05
		Accuracy (3)	M = −0.63, SD=,1.34				ns
		Visuo-spatial Memory Order irrelevant	M = −1.086, SD = 1.48				ns
		Order relevant	M = −1.556, SD = 1.83				<.05
		Verbal Fluency Task	M = 0.91, SD = 0.99				<0.001
Lowick et al. (2012) South Africa	60 children 5–6 yrs (30 HIV, 30 control)	GMDS-ER (Means) General Quotient	70		78.0		<.01
		Locomotor domain	75.7		82.7		<.01
		Personal-social domain	76.8		85.8		<.01
		Hearing-speech domain	60.6		66.9		<.05
		Eye-hand domain	77.3		82.8		<.05
		Performance domain	62.3		73.1		<.05
		Practical-reasoning	68.3		75.4		<.01
Maleea et al. (2011) USA & Puerto Rico	416 children 7–16 yrs (295 HIV, 121 affected)	BASC-2 Behavioural Symptoms Index	M = 51.5, SD = 10.2	M = 54.6, SD = 12.8	BASC-2 norms		<.05
		Emotional Symptoms Index	M = 49.1, SD = 9.3	M = 49.3, SD = 10.1			ns
Mellins et al. (2009) USA	340 children 9–16 yrs (206 HIV, 134 control)	DISC-IV Any psychiatric disorder	125 (60.7%)		66 (49.3%)		<.05
		Anxiety disorder	101 (49.0%)		55 (41.0%)		ns
		Mood Disorder	15 (7.3%)		7 (5.2%)		ns
		Behavioural Disorder	53 (25.7%)		32 (23.9%)		ns
		ADHD	37 (18.0%)		11 (8.2%)		<.05
		Substance Abuse	4 (1.9%)		8 (6.0%)		ns
Rice et al. (2012) USA & Puerto Rico	437 children 7–16 yrs (284 HIV+, 153 affected)	Clinical Evaluation of Language Functioning-Fourth Edition Primary (N = 48)	29 (10%)	19(12%)			ns
		Concurrent (N = 105)	67 (24%)	38 (25%)			
		None (N = 284)	188 (66%)	96 (63%)			
		Total (N = 437)	284	153			
Serchuck et al. (2010) USA & Puerto Rico	576 children 6–17 yrs (320 HIV+, 256 affected/control)	Wong Baker FACES					ns
		SF-MPQ *Pain In The Last 2 months*	130(41%)		82(32%)		<.05
		Males	34%		31%		ns
		Females	47%		33%		<.05
		Pain In The Last 2 Weeks	91(28%)		50(19%)		<.05
		Males	25%		14%		<.05
		Females	32%		25%		ns
		Duration >1 Week	64(20%)		28(11%)		<.05
		Males	14%		10%		ns
		Females	26%		11%		<.05
		Evaluated Odds Pain	1.07 (<.05)		1.08 (<.05)		
		Generalised Anxiety (GAD) Subject Caregiver	1.13 (ns)		1.22 (ns)		
		Major Depression (MDD)	1.15 (<.05)		1.08 (ns)		
		Subject Caregiver	1.14 (ns)		1.25 (ns)		
		Dysthymia (DD)	1.18 (<.05)		1.08 (ns)		
		Subject Caregiver	1.18 (ns)		1.31 (ns)		

Table 2 (*continued*)

Study	Sample	Cognitive measure	Score HIV	Score HIV affected	Score control	Score Other	P value (HIV + to controls)
Thomaidis et al. (2010) Greece	60 children 3–18 yrs (20 HIV+, 40 control) NA = Neuroimaging Abnormality	WISC-III & GMDS *General IQ Score* HIV+ without NA	M = 58.8, SD = 11.82		M = 78.0, SD = 18.2		ns
		HIV+ with NA	M = 82.4, SD = 18.8				<.05
		Practical IQ Score HIV+ without NA	M = 85.3, SD = 22.6		M = 78.5, SD = 21.6		ns
		HIV+ with NA	M = 57.6, SD = 15.0				<.05
		Verbal IQ Score HIV+ without NA	M = 80.5, SD = 14.9		M = 78.4, SD = 15.3		ns
		HIV+ with NA	M = 65.6, SD = 14.4				ns
		SDQ *Emotional* HIV+ without NA	M = 3.4, SD = 2.3		M = 2.4, SD = 1.7		ns
		HIV+ with NA	M = 2.2, SD = 1.1				ns
		Conduct HIV+ without NA	M = 1.7, SD = 1.5		M = 2.0, SD = 1.2		ns
		HIV+ with NA	M = 2.6, SD = 0.9				ns
		Hyperactivity HIV+ without NA	M = 4.3, SD = 2.9		M = 3.1, SD = 1.6		ns
		HIV+ with NA	M = 2.6, SD = 1.7				ns
		Peer problem HIV+ without NA	M = 2.5, SD = 1.6		M = 2.2, SD = 1.3		ns
		HIV+ with NA	M = 2.2, SD = 2.4				ns
		Prosocial HIV+ without NA	M = 8.5, SD = 1.6		M = 8.3, SD = 1.6		ns
		HIV+ with NA	M = 8.6, SD = 1.9				ns
		Total score HIV+ without NA	M = 11.7, SD = 6.6		M = 9.1, SD = 3.6		ns
		HIV+ with NA	M = 9.6, SD = 2.6				ns
Van Rie et al. (2008) Democratic Republic of Congo	160 children 18–72 months (35 HIV+, 35 affected, 90 control)	*Total No. of Children Mental*	35	35	90		<.0001
		No + Moderate	14(40.0%)	21(60.0%)	68(75.6%)		
		Severe	21(60.0%)	14 (40.0%)	22(24.4%)		
		Motor					<.0001
		No + Mild	25(71.4%)	30(85.7%)	90(100%)		
		Severe	10(28.6%)	5(14.3%)	0(0.0%)		
		Children 18–29 months Mental	11	13	20		<.0001
		No + Moderate	1(9.0%)	9(69.2%)	17(85.0%)		
		Severe	10(90.9%)	4(30.8%)	3(15.0%)		
		Motor					<.0001
		No + Mild	2(18.2%)	8(61.5%)	20(100.0%)		
		Severe	9(81.8%)	5(38.5%)	0(0.0%)		
		Children 30–72 months Mental	24	22	70		ns
		No + Moderate	13(54.2%)	12(54.5%)	51(72.9%)		
		Severe	11(45.8%)	10(45.5%)	19(27.1%)		
		Motor					<.0001
		No + Mild	23(95.8%)	22(100.0%)	70(100.0%)		
		Severely Delayed	1(4.2%)	0(0.0%)	0(0.0%)		
		Concurrent (N = 105)	67 (24%)	38 (25%)			
		None (N = 284)	188 (66%)	96 (63%)			
		Total (N = 437)	284	153			
Van Rie et al. (2009) Democratic Republic of Congo	160 children 18–71 months (35 HIV+, 35 affected, 90 control)	BSID, PDMS, SON *Cognitive Development* Visit 1 (baseline)	M = 65.8 ± 6.0	M = 74.8 ± 6.0	M = 84.6 ± 3.8		<.0001
		Visit 2 (6 months)	M = 75.8 ± 6.0	M = 74.9 ± 5.6	M = 87.3 ± 3.8		<.01
		Visit 3 (12 months)	M = 84.3 ± 7.2	M = 87.6 ± 6.6	M = 96.5 ± 5.0		<.01
		Mean Change of 1 to 2	M = 10.0 ± 5.7	M = 0.1 ± 5.2	M = 2.6 ± 3.6		ns
		Mean Change of 1 to 3	M = 18.5 ± 7.7	M = 12.8 ± 5.2	M = 11.8 ± 5.2		ns
		Motor Development Visit 1 (baseline)	M = 75.7 ± 4.2	M = 87.2 ± 4.2	M = 97.8 ± 2.6		<.0001
		Visit 2 (6 months)	M = 82.4 ± 4.0	M = 91.0 ± 3.8	M = 101.0 ± 2.6		<.0001
		Visit 3 (12 months)	M = 90.4 ± 3.8	M = 94.0 ± 3.6	M = 105.0 ± 2.6		<.0001
		Mean change of 1 to 2	M = 6.7 ± 3.8	M = 3.8 ± 3.6	M = 2.7 ± 2.4		ns
		Mean Change of 1 to 3	M = 14.6 ± 4.2	M = 6.8 ± 3.8	M = 7.6 ± 2.8		<.01

now needed. In the last five years, there have been enhanced resources and roll out of antiretroviral treatment as well as advances in identifying children and providing paediatric compounds. Even though treatment roll out to children may be lagging, it is unclear to what extent (if any) antiretroviral treatment itself affects cognitive outcome. Comparisons between children on treatment and those not yet receiving treatment may be needed, but clearly treatment decisions as well as compound choice are driven by medical need. Child development may be affected by many factors, including parental wellbeing, parental survival, parental employment, economic situation, parental mental health and level of stimulation within the home. There may well be a complex effect of HIV on some or all of these factors which can specifically affect the environment and thereby the cognitive development of children with HIV.

Given these changes, an updated review was conducted to explore developmental effects of HIV including cognitive, behavioural, developmental and psychological function as measured by the various studies and standardised child developmental inventories. The review covers studies on effects of HIV for the period 2008 to 2013. The review also aims to provide a more detailed understanding of concepts under the cognitive development umbrella such as language development, motor skills, memory, executive function, spatial abilities, information processing and other cognitive processes that would affect how a child gains access to their learning curriculum and functions in the emerging adult world.

2. Method

In January 2013 we searched the online databases of Medline, PubMed, PsycINFO, the Cochrane database and follow up references. Search terms were informed by the initial systematic review (Sherr et al., 2009). Search terms were varied to adapt to the requirements of the different databases. The search terms included HIV, child, various forms of child (such as infant, minor, baby new-born), cognitive, psychosocial, emotional development, neurological function, intellectual learning language or memory and explored control and comparison group provision (see Appendix A for specific search criteria and number of results at each stage). The aim was to abstract data from the studies of competent design, to track the level of neurocognitive development effect, to explore measurement tools used, to log demographic variables in terms of study sites, to examine whether different domains of functioning are studied and to consider the nature and quality of comparison and control groups in order to establish causal pathways in terms of HIV infection on cognitive development.

2.1. Inclusion and exclusion criteria

Papers were restricted to English language publications and were included if they provided empirical data on HIV infected children with a control or comparison group—either HIV exposed but uninfected children (affected) or uninfected unexposed controls. To meet inclusion criteria studies had to report a cognitive, developmental or mental health measurement for both groups. Non primary data, review articles and opinion pieces were excluded. After the search was conducted, papers were read by a team of three psychologists for confirmation of inclusion. The lead author took responsibility for adjudication in cases of non-agreement. The search was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations which sets out design and study characteristics for grading of quality (CRD, 2009). The details of the papers were extracted and entered into common tables listing the full reference, the country of study, the method, population and group details, listing of each measure and main findings were contrasted for the HIV infected group compared to various comparison groups. Due to the heterogeneity in the studies, different methods and the use of a wide range of inventories to measure components of cognitive or developmental parameters, we were not able to combine results into a meta-analysis.

The search (see Fig. 1) generated 1739 hits. After excluding duplicates and non-relevant items (books and non-English articles) 1657 remained for more detailed exploration of full title and abstract of which 1594 were excluded on abstract screening as not eligible or not relevant to the topic under study. The remaining 63 papers were read in full, except for 7 that were inaccessible. References from these papers were followed up, generating a further 2 papers for full text reading. From this phase, 11 were excluded on the grounds of inadequate or irrelevant data, no HIV infected group, no control group or no cognitive/psychological functioning outcomes and 1 was an intervention study. Of the remaining papers, 26 were excluded as they were originally published before 2008. Twenty-one published studies were included and were subjected to detailed data abstraction.

3. Results

3.1. Study characteristics

The highest percentage of data was from Africa (7 studies; 33%) with 24% from the USA, 19% Puerto Rico, 10% Europe (Ukraine, n = 1, Holland, n = 1, Greece, n = 1) and 10% from Asia. The studies characteristics are set out in Table 1 below. The table provides the study, place, sample characteristics and measures used. Findings are then coded for each study into 3 categories, "no differences reported, detrimental effect of HIV reported and mixed findings".

Of the 21 studies, 5 compared HIV positive children with those who had been born to an established HIV positive mother but were virus free and HIV negative themselves (referred to as "seroreverters" or HIV affected). Four compared HIV positive children with HIV affected as well as including a second, HIV negative control—namely children who had not been exposed to HIV in utero. Eight studies compared HIV positive children with a negative control group and 2 compared HIV positive with a control group and other illnesses such as asthma and hematologic/oncological diseases. These studies were able, therefore, to control for HIV virus as well as exposure to HIV in utero and living with an HIV positive mother. Two studies compared HIV positive children with 'normative means'. Overall the studies report on 4237 children; 2023 HIV positive, 727 HIV negative but exposed in utero, 1307 control unexposed and uninfected children, 91 status unknown and 89 with other illnesses) (see Table 2).

The age ranges in the studies were varied from infants (one month) to 18 year olds. Two studies provided no exact detail on age ranges; they did however provide a mean or median age. The age ranges make comparisons difficult, due to the fact that there are different abilities and measures across the different ages and very few measures are standardised across age groups. Over half the studies (12/21) sampled children between the age ranges of 5–18 years, with various inclusion ages. Six (6/21) studies included children between 6 and 17 years; two included 7–16 year old children, one was confined to 5–6 year olds, two included 9–16 year olds, one 8–14 year olds and one 3–18 year olds. Fewer studies included children from younger age bands. Three studies included children as young as 18 months, one included children from 1 month and one included children as young as 6 months old. On the whole the data is mostly available for older children with considerable gaps in the early crucial age bands.

3.2. Measurement tools used

There are a wide range of tools available to measure different components of cognitive performance. These vary in the design, content and validation in different cultures. The measurement scales used are listed in Table 3. This review shows that across the 21 studies, 31 different

Table 3
Standardised scales and measures utilised in studies.

Measures	Occasions used
1. Amsterdam's Neuropsychological Tasks (ANT) Program tests	1
2. Bayley Scales of Infant Development 2nd Edition (BSID-II)	4
3. Behaviour Assessment System for Children, 2nd edition (BASC-2)	2
4. Social and Academic Functioning Questionnaire	1
5. Child and Adolescent Symptom Inventory (CASI)	3
6. Child Behaviour Checklist (CBCL) (Thai Version)	1
7. Child Self-Report inventory (CSI)	3
8. Clinical Evaluation of Language Functioning-Fourth Edition (CELF-4)	1
9. CT/MRI scan	1
10. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)	1
11. Diagnostic Interview Schedule for Children (DISC-IV)	1
12. Emotional Availability Scales (EAS)	1
13. Global Intelligence Test	1
14. Griffiths Mental Development Scales (GMDS)	2
15. Kilifi Developmental Inventory (KDI)	1
16. Peabody Test, Third Edition (PDMS-III)	5
17. Rossetti Infant–Toddler Language Scale (RITLS)	1
18. Short-Form McGill Pain Questionnaire (SF-MPQ)	1
19. Snijders–Oomen Nonverbal Intelligence Test (SON-R)	4
20. Standardised Test for Thai Children	1
21. Strange Situation Procedure (SSP)	1
22. Strengths and Difficulties Questionnaire (SDQ)	1
23. Symptom Inventory (SI-4)	1
24. The Children's Affective Representations of Relationships Scale (CARRS)	2
25. The Friendship Interview	1
26. The Friendship Quality Questionnaire (FQQ-R)	1
27. Verbal Fluency Task	1
28. Wide Range Achievement Test, Third Edition (WRAT-3)	1
29. Wong Baker FACES	1
30. Wechsler Intelligence Scale (WISC)	5
31. Youth Self-Report inventory (YI)	3

tools to measure cognitive development were used. Some studies used multiple measures. The Bayley Scales of Infant Development (BSID) (Bayley, 1993) were used in 4 studies (19%). Other scales used included the Snijders–Oomen Nonverbal Intelligence Test (SON; Tellegen, Winkel, Wijnberg-Williams, & Laros, 1998), the Wide Range Achievement Test (WRAT; Jastak & Jastak, 1965), the Wechsler Scales (WISC; Wechsler, 1991; Kaplan, Fein, Maerlander, Morris, & Kramer, 2004), The Child Behaviour Checklist (CBCL Thai version; Achenbach & Ruffle, 2000), the Griffiths Scales (GMDS; Griffiths, 1970) and Rossetti Infant–Toddler Language Scale (RITLS; Rossetti, 1990). These were supplemented by an array of functioning tests, standardised neurological examinations e.g. CT/MRI scans, school measurements such as the caregiver completed social and academic functioning questionnaire (Gadow, DeVincent, & Schneider, 2008) and anthropometric measures such as weight, height, and head circumference which reflect on development in terms of growth.

3.3. Human immunodeficiency virus and neurocognitive development

The majority of the studies (17/21) (80.1%) showed that HIV was associated with some form of detrimental effect on cognitive development, across a wide range of different measures. Eight studies (38%) reported detrimental effects on all measures and a further 10 (totalling 48%) reported detrimental effects on at least one measure. Of these eight, seven emanated from Sub-Saharan Africa. Only three studies found no significant differences or effects of HIV between the HIV positive group and a comparison group (14%). The data from each measure on the 21 studies are summarised in Table 2.

3.3.1. Language

Seven studies provided specific data on language scores. Baker, Niec, and Meade (2012) and Brackis-Cott, Kang, Dolezal, Abrams, and Mellins (2009) used the Peabody Picture Vocabulary test (PPVT; Dunn & Dunn, 1965). Most studies were conducted in the USA: Baker et al. (2012) compared 70 positive, exposed and asthmatic 8–14 year old children whereas Brackis-Cott et al. (2009) compared 325 HIV positive and negative 9–16 year old children. Koekkoek, De Sonneville, Wolfs, Licht, and Geelen (2008) used the verbal fluency sub test of the SON on 22 HIV positive children with a median age of 9.46 in Amsterdam comparing them to "norms". There were no significant language differences on the Baker et al. (2012) study, but the other two studies found significantly lower language scores for the HIV positive children. Rice et al. (2012) carried out a comprehensive language assessment linking this with hearing impairment and environmental variables on 437 HIV positive and affected 7–16 year old children in the USA and Puerto Rico. They found elevated language impairment among both HIV positive and HIV affected children (40% prevalence rate which is much higher than the 16% expected rate based on country norms).

3.3.2. Cognitive/executive functioning categories

Only one study explored pattern recognition as a specific sub-item (Koekkoek et al., 2008) and found HIV positive children significantly lower in both speed and accuracy than "norms". Executive function is usually measured by attention variables, visuo-spatial abilities and working memory. Koekkoek et al. (2008) found that executive functioning and processing speed were specifically challenged for HIV positive children.

3.3.3. Measure of global development (mental and motor)

The main measure of global development was the BSID. These scales generate a motor and a mental development score. However, different researchers utilised the scores differently to examine relative performance, proportion that were delayed or proportion with significant delay. Van Rie, Dow, Mupuala, and Stewart (2009) studied 160 18–71 month old children in the Democratic Republic of Congo (DCR) with baseline and two follow up measures and showed that the HIV positive children had lower mean scores than both control groups (HIV affected and HIV unaffected) at all three time points for both motor and mental development. Van Rie, Mupuala, and Dow (2008), appearing to use the same sample as Van Rie et al. (2009), explored the severity of delay in a study of 160 children (35 HIV positive, 35 HIV affected and 90 controls) who were clustered into three age bands (18–72 months; 18–29 months and 30–72 months). They found significantly more HIV positive children were severely delayed (60% versus 40% in the affected group and 24.4% in the control group) on mental development in the first age group. The pattern was repeated for motor delay with 28.6% of the HIV positive children delayed compared to 14.3% of the affected children and none of the control children. Of interest was that the differences seemed to dissipate over the time periods (significantly worse at the second time period, but a trend at the third). Baillieu and Potterton (2008) studied 40 18–30 month old HIV positive children in South Africa and found significantly lower cognitive development than the children's cognitive development for their chronological age in 97.5% of the sample. Ferguson and Jelsma (2009) studied 86 1–33 month old HIV positive and healthy children in South Africa (51 HIV positive, 5 affected and 20 HIV status unknown) and found that significantly more HIV positive children were "significantly delayed" compared to the healthy children (66.6% versus 5.7%).

3.3.4. Behavioural challenges

These were measured in diverse ways across the studies. Baker et al. (2012) showed lowered mean scores on the children's affective representation of relationship scale (CARRS; Baker & Niec, 2007) as well as the emotional investment and the behavioural assessment system for children (BASC; Reynolds & Kamphaus, 2004) compared to control children, but none of these measures reached statistical significance. Similarly Ananworanich, Jupimai, Mekmullica, Sosothikul, and Pancharoen (2008) did not find any differences on elements of the CBCL Thai version which examines internal and external behaviours. Ananworanich et al. (2008) study involved 257 primary caregivers of 6–16 years old HIV positive, HIV negative and children with hematologic/oncologic

diseases in Thailand. Isaranurug and Chompikul (2009) showed with 388 6–12 years old Thai children (74 infected, 223 not infected and 91 status unknown) that there were no differences on sensitivity to others, acceptance of criticism, adaptation, expressiveness, self-esteem or cheerfulness but the HIV positive children had significantly lower self-control and quick recovery. Chernoff et al. (2009) also showed, with 557 HIV positive or exposed/living with someone with HIV American children aged 6–17, no significant overall mood problems on items such as ADHD, aggression or anxiety. The authors also found they had equal prevalence of psychiatric symptoms, but that the HIV positive were more likely to receive medication and behavioural treatment. Baker et al. (2012) also compared children with asthma to those with HIV on measures of social functioning and friendship quality and found the HIV positive children to have better outcomes which they attributed to comprehensive multidisciplinary services and support which buffer against stressors and may in fact facilitate positive outcomes. This USA study may set a precedent for service provision needs in other geographical regions.

3.3.5. Gender

Nineteen of the 21 studies (90%) provided data on distribution of child gender (see Table 1); however, only 6 studies (29%) proceeded to analyse by gender. Maleea et al. (2011) compared 416 7–16 year old children (295 HIV positive perinatally infected, 121 affected) in the United States and Puerto Rico on mental health functioning. No gender differences emerged on either the Behavioural Symptoms Index (BSI) or Emotional Symptoms Index (ESI) (BASC; Reynolds & Kamphaus, 2004) for the entire group. Gender differences were found when results were stratified by infection. HIV affected males were more likely than females to have elevated BSI scores (37% versus 18%) and HIV positive females were more likely than HIV positive males to have elevated ESI scores (18% versus 5.9%). Serchuck et al. (2010) compared 576 6–17 year old children (320 HIV positive, 256 HIV negative) in the United States and Puerto Rico on the prevalence of pain and psychiatric symptoms. Among males, there was a higher prevalence of pain during the last two weeks for HIV infected than controls (25% vs 14%). HIV positive females had significantly higher rates of pain compared to control females during the last two months (46% vs 33%) and a higher proportion with pain of more than one-week duration (26% more vs 11%). Baker et al. (2012) found across their entire sample (HIV positive, control and asthmatic children), girls scored significantly higher than boys on the emotional investment in relationships scale (CARRS) ($M = 54.05$, $SD = 1.27$; $M = 48.98$, $SD = 1.09$ respectively). Gadow et al. (2012) compared 573 6–17 year old children (296 HIV positive perinatally infected, 229 affected/living with HIV positive person) in the United States and Puerto Rico on emerging mental health concerns. They found that across both groups the odds of emerging depression (OR 2.13 (CI 1.16, 3.91)) and anxiety (OR 2.34 (CI 1.26, 4.38)) symptoms occurring in females were higher than males. Rice et al. (2012) found within their 7–16 years old HIV positive group, males or children who had a biological parent as caregiver had significantly lower odds of having a language impairment as well as a cognitive or hearing impairment. Ananworanich et al. (2008) found that in their sample of 6–16 years old Thai children females had more delinquency problems than males ($p = .007$) across the entire sample (HIV positive children, control children and children with haematologic/oncologic diseases).

3.3.6. Effects of treatment

Very few studies examined the effect of treatment on cognitive outcome. Koekkoek et al. (2008) noted that higher CD4 count at initiation of HAART and duration of such treatment were both associated with improved working memory function and attention control. Four of the studies (19%) specified whether any of the mothers were on treatment while they were pregnant (see Table 4). Forty-one percent of the mothers were receiving treatment in Rice et al. (2012) study in the United States and Puerto Rico whereas only 24.5% of mothers were on treatment in Maleea et al. (2011) study also in the US and Puerto Rico. Ferguson and Jelsma (2009) showed 18% of the children in the HIV positive sample had been exposed to PMTCT prophylaxis whilst in utero. None of the HIV positive mothers were receiving treatment in Van Rie et al. (2009) study. Only 3 studies (14%) did not state whether the HIV positive children were receiving antiretroviral treatment. Another 3 studies included HIV positive children who were not receiving treatment: 1 to 33 month old children in South Africa (Baillieu & Potterton, 2008), 6–13 month old children in Kenya (Abubakar, Holding, Newton, Van Baar, & Van de Vijver, 2009) and 18–72 month old children in the Democratic Republic of the Congo (Van Rie et al., 2008). All the other studies included HIV positive children receiving treatment ranging from 66.6% in South Africa (Ferguson & Jelsma, 2009) to 100% (Baker et al., 2012; Jelsma, Davids, & Ferguson, 2011; Lowick, Sawry, & Meyers, 2012; Thomaidis et al., 2010). Two of the studies, with all the HIV positive children receiving antiretroviral treatment, were from South Africa (Jelsma et al., 2011; Lowick et al., 2012), one was from Greece (Thomaidis et al., 2010) and one was in the United States (Baker et al., 2012).

3.3.7. Cognitive delay is not universal

Fifteen of the studies presented results which showed how many HIV positive children did not have any cognitive effects (see Table 4). Six studies found, on at least one measure, the percentage of children not affected was 10% or less. Baillieu and Potterton (2008) found only 2.8% of HIV positive children in their sample had a cognitive developmental age not lower than the chronologically age of the sample. Only 9.8% of the HIV positive children from South Africa in Ferguson and Jelsma's (2009) study had motor performances within the normal limit. Of the children who received antiretroviral treatment (34 children) only 8.82% had a motor performance within the normal limit. No females aged 12–16 in Ananworanich et al.'s (2008) study were in the normal range for the CBCL Thai version although all of the male participants were. None of the male participants aged 12–16 had a normal score on the somatic variable of the CBCL whereas 50% of the female participants did. Lowick et al. (2012) found, in their study in South Africa, only 3 children overall (10%) were in the total normal range using the GMDS (Griffiths, 1970). Over 70% of the children were in the normal range for the social-personal domain and over 50% had no deficits in the locomotor domain. Thomaidis et al. (2010) found, in a sample of 3–18 year olds in Greece, 0 of the 5 HIV positive children with neuroimaging abnormalities (NA) had a normal general, practical or verbal IQ score whereas 40%, 33.3% and 40% of the HIV positive children without NA had a normal score respectively. Van Rie et al. (2008) found for the HIV positive children aged 18–29 months 0% had no mental developmental delay and only 9% (one child) had no motor developmental delay. Children aged 30–72 months had higher levels of children not having mental or motor delay: 20.8% and 41.7% respectively. All children were preschool aged children from the DRC.

Nine studies found, on at least one measure, the percentage of children with no cognitive deficits to be 80% or greater. Three of these studies found 10% or less of children to be in the normal range on at least one measure (Ananworanich et al., 2008; Baillieu & Potterton, 2008; Thomaidis et al., 2010) highlighting HIV may be affecting specific subdomains. Baillieu and Potterton (2008) found no fine motor delay in 87.5% of their sample. Thomaidis et al. (2010) found that 80% or more of the HIV positive children, both with and without neuroimaging abnormalities, were in the normal range for emotional, conduct, peer problems, prosocial scales and the total score on the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Only the HIV positive children with neuroimaging abnormalities were in the normal range for the hyperactivity scale on the SDQ. Ananworanich et al. (2008) found that 80% or more of male and females aged 6–11 were in the normal range for anxiety, depression, delinquency, hyperactivity and aggressiveness scales on the CBCL. Eighty-seven percent of the females were also in the normal range on the social withdrawal

Table 4
Antiretroviral treatment (mother and child) and children with no delay.

Study	Mother on treatment	Child on treatment	No. of children with no cognitive delay
Abubakar et al. (2009)	Not given	N	Only mean scores given
Ananworanich et al. (2008)	Not given	Not given	*6–11 year olds* *CBCL* M 45% F 61% normal score; *Anxiety* M 90% F 94% normal score *Somatic* M 45% F 52% normal score *Depression* M 87% F 94% normal *Social Withdrawal* M NA F 87% normal External %—*Immaturity* M 52% normal score F NA *Delinquency* M 97% F 84% normal *Hyperactivity* M 87% F90% normal *Aggressive* M 97% F 94% normal *12–16 year olds* *CBCL* M & F 100% normal score *Anxiety* M & F 100% normal score *Somatic* M 0% F 50% normal score *Social Withdrawal* M & F 100% *Immaturity* M 50% normal score *Delinquency* M & F 50% normal *Aggressive* M 50% F 100% normal score
Baillieu and Potterton (2008)	Not given	N-antiretroviral therapy naive	No gross motor delay in 15%; No fine motor delay in 87.5% No global language delay in 17.5%; Cognitive developmental age not lower than chronological age in 2.5%
Baker et al. (2012)	Not given	Y-21 children on antiretroviral medication (100%)	Only mean scores given
Brackis-Cott et al. (2009)	Not given	Y-84% on HAART	38% not below average language receptive ability score. 46% did not score below average on word recognition. 63% not kept in school.
Chernoff et al. (2009)	Not given	Y-81% on HAART	*Screening prevalence (assessed by child or caregiver)* 125 (39%) did not meet criteria for any problems 263 (82%) did not meet criteria for ADHD 274 (86%) did not meet criteria for aggression 264 (83%) did not meet criteria for mood disorder 200 (63%) did not meet criteria for anxiety disorder *Impairment (assessed by caregiver)* 273 (85%) did not meet criteria for any problems 281 (88%) did not meet criteria for ADHD 300 (94%) did not meet criteria for aggression 315 (99%) did not meet criteria for mood disorder 302 (95%) did not meet criteria for anxiety disorder *Impairment and screening prevalence (assessed by child or caregiver)* 264 (83%) did not meet criteria for any problems 282 (88%) did not meet criteria for ADHD 299 (94%) did not meet criteria for aggression 310 (97%) did not meet criteria for mood disorder 310 (97%) did not meet criteria for anxiety disorder
Dobrova-Krol et al. (2010)	Not given	Y-18/20 received the same anti-retroviral medications.	In the HIV infected group, 44% of family-reared children were found to demonstrate secure attachment. For HIV-infected institution-reared children: 31% were found to demonstrate secure attachment. Only mean scores given for the rest of results
Ferguson and Jelsma (2009)	Y – 18%	Y-34 (66.6%) on ART	9.8% had motor performance within normal limits. Of those receiving ART (n = 34), 8.82% had motor performance within normal limits. Of those HIV infected children exposed to antiretroviral prophylaxis (n = 20), 10% had motor performance within normal limits. Of the participants on ART for <6 months (n = 17), 5.88% had motor performance within normal limits and of those on ART >6 months (n = 17) 11.76% had motor performance within normal limits.
Gadow et al. (2010)	Not given	Y-(66%) highly active antiretroviral treatment (HAART) with protease inhibitors, and 15% HAART without PI	88% did not meet criteria for attention-deficit/hyperactivity disorder 95% did not meet criteria for oppositional defiant disorder 99% did not meet criteria for conduct disorder 98% did not meet criteria for generalised anxiety disorder 99% did not meet criteria for separation anxiety disorder 98% did not meet criteria for depressive disorder 99% did not meet criteria for manic episode No psychotropic meds (ever) N = 245; 77% (current)N = 276; 87% No behavioural therapy (ever) N = 235; 73% No therapy (ever) N = 203; 63% No special education (ever evaluated for) N = 183; 56%
Gadow et al. (2012)	Not given	Not given	31% no Symptom Cutoff score for at least 1 targeted disorder. *Any disorder*—31% did not meet criteria at screening cutoff 76% did not meet criteria at clinical cutoff 77% did not meet criteria at impairment cutoff *ADHD*—75% did not meet criteria at screening cutoff 84% did not meet criteria at clinical cutoff 84% did not meet criteria at impairment cutoff *Disruptive behaviours*—78% did not meet criteria at screening cutoff 88% did not meet criteria at clinical cutoff 89% did not meet criteria at impairment cutoff *Depression*—79% did not meet criteria at screening cutoff 96% did not meet criteria at clinical cutoff 94% did not meet criteria at impairment cutoff *Anxiety*—76% did not meet criteria at screening cutoff 89% did not meet criteria at clinical cutoff 96% did not meet criteria at impairment cutoff
Isaranurug and Chompikul (2009)	Not given	Not given	Only mean scores given

(continued on next page)

Table 4 (*continued*)

Study	Mother on treatment	Child on treatment	No. of children with no cognitive delay
Jelsma et al. (2011)	Not given	Y-100% (23 children)	Only mean scores given
Koekkoek et al. (2008)	Not given	Y-18 HAART and 2 new commenced	Only mean scores given
Lowick et al. (2012)	Not given	Y-30 HIV-infected preschool children (stable on ART for more than one year) (100%)	Total overall N = 3, 10%; Locomotor domain N = 16, 53.3% Personal-social domain N = 22, 73.3%; Hearing-speech domain N = 3, 10%; Eye-hand domain N = 15, 50%; Performance domain N = 11, 36.7%; Practical reasoning domain N = 9, 30%
Maleea et al. (2011)	Y-60; 24.5%	Y-278; 94.2% on HAART	62% with no mental health problems. 230; 71.1% did not meet criteria for any psychiatric diagnosis. 81% with no caregiver reported behavioural problems in the at-risk or clinically significant range. 88% did not report emotional problems in the at-risk or clinically significant range.
Mellins et al. (2009)	Not given	Y-194; 84% on HAART	N = 81; 39.3% did not meet criteria for any psychiatric disorders N = 105; 51% did not meet criteria for anxiety disorder N = 191; 92.7% did not meet criteria for mood disorder N = 153; 74.3% did not meet criteria for behavioural disorder N = 169; 82% did not meet criteria for ADHD N = 202; 98.1% did not meet criteria for substance abuse
Rice et al. (2012)	Y-180; 41%	Y-252 HAART, 13 ART (93%)	284; 61% had no language impairment
Serchuck et al. (2010)	Not given	Y-81% HAART	59% reported no pain in the last 2 months. 72% reported no pain in the last 2 weeks., 80% did not report pain lasting more than one week.
Thomaidis et al. (2010)	Not given	Y-11 on HAART and 9 on HAART and AZT. 100% of HIV positive	*SDQ results (HIV positive with normal scores)* *Emotional* HIV without NA—N = 12, 80%, with NA—N = 5, 100% *Conduct* HIV without NA—N = 13, 86.7%, with NA—N = 4, 80% *Hyperactivity*, HIV without NA—N = 10, 66.7%,with NA—N = 5, 100% *Peer problems* HIV without NA—N = 14, 93.3%, with NA—N = 4, 80% *Prosocial*,HIV without NA—N = 14, 93.3% with NA—N = 5, 100% *Total score*—HIV without NA—N = 11, 73.3%, with NA—N = 5, 100% *IQ (HIV positive with normal scores)* *General* HIV without NA—N = 6, 40% with NA—N = 0, 0% *Practical IQ score* HIV without NA—N = 5, 33.3% with NA—N = 0, 0% *Verbal IQ score* HIV without NA—N = 6, 40% with NA—N = 0, 0% **NA = Neuroimaging abnormalities*
Van Rie et al. (2008)	Not given	N-ART-naive or <1 week HAART before assessment.	*All children (18–72 months)* No mental development delay N = 5, 14.3%,; No motor development delay N = 11, 31.4% *Children 18–29 months*; No mental development delay N = 0, 0% No motor development delay N = 1, 9% *Children 30–72 months*—No mental development delay N = 5, 20.8% No motor development delay N = 10, 41.7% *No language comprehension delay* N = 3, 23.1% *No language expression delay* N = 2, 15.4%
Van Rie et al. (2009)	N	Y-71% on HAART	Only mean scores given

scale. In the older category (12–16), 80% or more of both sexes were in the normal range for the anxiety and social withdrawal scales on the CBCL. All males were in the normal range for the overall score and all females were in the normal range for aggression.

4. Discussion

The 2009 review showed the growing evidence on cognitive challenges in HIV. In contrast the updated review captures the shift of studies from the USA to sub-Saharan Africa, the deeper understanding of cognitive challenges and the complexity of effects. Sixty-six percent of studies were from the USA in 2009 and this has reduced to 43%, reflecting the reality that the majority of HIV positive children live in Sub-Saharan Africa and the attention which is now being focussed on this group. Although there is a literature on gender and cognitive functioning in the non-HIV arena, too few studies analysed their data by gender to give full insight into gender variation to guide programmes and interventions.

The studies identified in the update show more complex design including a greater array of measures with a broader coverage of cognitive domains. These serve to initiate insight into a more complex understanding of cognitive performance, development and behavioural concepts usually included under the broad scope of cognitive function. The broad areas of challenge for children with HIV infection are becoming clear. The review describes how children with HIV infection show a delay in a number of domains. This holds true across various different comparison groups. HIV negative children born to HIV positive mothers provide a comparison group for some studies. This controls for HIV infection in the household, HIV exposure in utero and even possibly ART exposure. This data seems to identify the importance of direct viral implications in cognitive development and a future area of study. In relation to the behavioural components of child functioning, the picture is somewhat complex. Although behavioural problems were noted in some studies, they were not found in all. Indeed in some (Baker et al., 2012) the asthma group had more social interaction difficulties as it appears that the HIV positive children have benefited from sustained support. The spotlight, however, may have different effects. Chernoff et al. (2009) noted that HIV positive children had equal prevalence of behavioural challenges to comparison children, but were more likely to be treated with medication or behavioural interventions. The environment within which the children are raised seems to be an important factor in the course of their developmental outcome. This was highlighted in a study by Dobrova-Krol, Bakermans-Kranenburg, Van IJzendoorn, and Juffer (2010) who cautioned that the presence of institutionalised rearing was associated with negative outcomes more so than HIV status. The wide range of economic and social environments for children may need to be controlled more carefully in future studies, given the independent contributions of environment on child outcome. As the vast majority of children with HIV reside in Africa, clarity is needed about the extent to which studies from other settings generalise. Cognitive delay risks may be a compound challenge to children in the HIV era who risk

exposure to the virus, parental death and institutionalised care—all independently associated with developmental delay.

More recent studies are providing more detailed explanations and ways of exploring and predicting cognitive challenges and specific deficits. For example Thomaidis et al. (2010) commented on the importance of neuroimaging abnormalities in outcome and differentiated the outcomes for those with and without abnormalities. Cognitive performance may be affected by multiple variables. Ferguson and Jelsma (2009) noted that in addition to different outcome scores, children with HIV also had significantly more hospital admissions, single parents and differences in housing environments. These intervening variables may contribute to cognitive development via environmental stimulation and learning opportunity. Serchuck et al. (2010) noted the importance of pain as a mediator in performance. Thus any study purely concentrating on cognitive variables may miss such mediators. Nutrition was seen as a factor to be considered indirectly as height and weight measures interacted with performance (Isaranurug & Chompikul, 2009). Environment, parenting and stimulation also appeared to be a factor to consider in child cognitive development. Jelsma et al. (2011) reported on poor stimulation in environments when comparing both foster care and institutional care for HIV positive children. Maleea et al. (2011) noted that children with HIV had more problems than comparison exposed but uninfected children, but reported that caregiver characteristics were associated with higher odds of problems, including psychiatric disorder, limit setting problems and health related functional limitations.

More than 2.3 million children younger than 15 years old are living with HIV, of which 90% are living in Africa (WHO pediatric adovacy toolkit, 2011). Without access to HIV care and treatment, every day almost 800 HIV positive children die. Only 28% of children who require treatment are receiving it compared to 37% of adults. In some African countries the disparity between children and adults on treatment is greater (WHO pediatric adovacy toolkit, 2011). In terms of cognitive performance, there are two ways in which antiretroviral treatment may work. Firstly, the treatment may stop future infections preventing less hospitalisation for HIV positive children and therefore they have increased availability of learning. The second possible way is that the treatment may reduce viral load directly. In the adult literature (Best et al., 2009), choice of compounds seems to be important given differential rates of brain barrier permeation (Koopmans, Ellis, Best, & Letendre, 2009) found in adult studies, but not yet examined in children.

In the systematic review antiretroviral treatment should be considered in terms of its effects and relationship to cognitive performance. One study pointed out that CD4 count at initiation of treatment was a predictor of cognitive performance, as was duration of treatment (Koekkoek et al., 2008). The evidence on the effects of antiretroviral are mixed. Jelsma et al. (2011) reported that antiretroviral treatment did not result in restoration of performance. Lowick et al. (2012) noted a 7.9 fold increase in severe delay in HIV infected children compared to control children. Brackis-Cott et al. (2009) reported that for a youth sample those taking medication had lower WRAT-3 scores. Of the six studies that had 10% of the HIV positive or less in the normal range on at least one measure, two studies samples were 100% antiretroviral naïve and one did not specify. All HIV positive children in another two studies were on treatment. In one study they were on treatment for a year and in the other they did not specify the length of treatment. Another study had a sample of 66.6% of HIV positive children on treatment but they also do not specify the length of time on treatment. Clearly such studies are not comparable. Research shows that being on combination antiretroviral therapy for a year is associated with modest improvements in neurocognition in particular attention, processing speed and executive performance (Antinori et al., 2013) thus information on initiation and duration of treatment in necessary, as well as more detail on the type of regimen and those containing protease inhibitors. Van Rie et al. (2009) showed the importance of early intervention in children, with the most gains shown in the early presenters. This study also shows the importance of longer term follow up rather than cross sectional data in order to understand the course of cognitive development. It is unclear in this study which component of the intervention can be linked to the improvements that were seen over time, as children were provided with treatment for opportunistic infections, access to nutritional programmes and highly active antiretroviral treatment as appropriate. However, it is also important to look at loss to follow up, as the longer term studies may lose the most severely ill children and thus skew the data.

The quality of the data severely hampers clear insight into the true prevalence of delay, the causal pathways and the options for remediation. Multiple measures are used across a wide age span and thus meta-analysis and data pooling of any sort is difficult. Even within the same measures, different studies use the data in different ways—such as absolute scores, or percentage and proportion with severe delay. Furthermore when standardised scales are translated or adapted they need to be revalidated—few studies report on such attention to detail. Few studies are able to control for many of the variables that may also contribute to the presence and course of delay over time. Longitudinal studies are rare and cross sectional studies have limitations. Some studies (example Van Rie et al., 2008) look at different age cohorts and find that "young HIV infected children performed worse". This may be a sampling issue where children with severe disease, in the absence of treatment, do not survive into the older age groups and this disproportionately affects the range of scores among surviving children. Van Rie et al. (2008) found the proportion of children with missed follow up visits was higher among the younger than older children. In particular in the infected children, only 5 out of the 11 younger children attended the 2nd or 3rd follow-up visit whereas 22 out of 24 of the older children attended the follow up. The majority of missed visits were due to 7 children who died. Those who are more likely to survive may have the least effects. Ceiling effects may have also been present. For example, the study by Ananworanich et al. (2008) noted high levels of behavioural problems among all groups in their study which compared HIV positive children with those diagnosed with haematological/oncological disorders. Exposure to antiretroviral treatment may differ with the HIV positive children less likely to be exposed to maternal HAART, than the uninfected HIV exposed infants. Other treatment factors may also interact with cognitive performance (such as medication for psychiatric or other health conditions). Thus claims about group improvements over time should be viewed with caution and only after data is adjusted for those who do not survive. Within all the studies, the use of group mean scores make it difficult to know if all the children are performing under a certain level, or if a small subgroup of children are performing particularly poorly and affecting the total mean. This detailed information would specifically assist in targeting care, and appreciating if a large number of children needed help with relatively small problems, or if a smaller group of children needed intervention with widespread severe problems (or both).

Policy for children in this area is urgently required. For adequate and appropriate HIV management, it is vital to test and establish the HIV status of each child. In 2009, an estimated 1.4 million HIV exposed infants were born but only 6% received early infant diagnosis services. Infants who are tested may not receive their results and only a third who test positive initiate ART (WHO pediatric adovacy toolkit, 2011). Treatment rollout to all children is urgently needed. Information on the neuroproperties of treatment on children is also required. In adults, ART distribution and effectiveness in the Central Nervous System (CNS) varies substantially between different compounds and individuals. ART that has better neuroeffectiveness may improve or prevent HAND (Letendre et al., 2008). Guidelines in this area need to include specific instructions on children.

Children have the right to education and this data clearly indicates a need for more special education provision for HIV positive children. Studies do show that targeted interventions are available to enhance

capabilities (Klasen & Crombag, 2013; Ross, Dorris, & McMillan, 2011). With treatment HIV Positive children are growing up and reaching adolescence. If their decision-making skills are compromised HIV management and risk reduction may be hampered if they face specific challenges with partnership and risk negotiation, HIV status disclosure and risk behaviour reduction. Interventions to improve cognitive skills is of benefit in its own right and additionally may help with many of the decision making skills needed for safe sex and behavioural change that play a role in spreading the infection. Cognitive development, overall, is a neglected area of study and provision. Baseline and repeated measures are not routinely collected and repeated for children. Clinic staff should be trained to respond to a child with cognitive deficits. The area has moved forward for adults, but assessment and treatment for children lags behind. The review has identified a need for researchers to harmonise measures to improve research in this area.

The review highlights the need to examine HIV positive children who do not have any cognitive deficits to understand predictors of performance and to guide interventions and prevention initiatives. If we are able to identify these children, is it possible to transfer the resilience skills to others? Of the six studies which included 10% or less of HIV children without delay, four were in sub-Saharan Africa (3 in South Africa) of which two included children who were not receiving antiretroviral treatment. Of the nine studies with at least one measure, where 80% or more children had no deficits only one was from sub-Saharan Africa and six (66%) almost exclusively USA based. Three studies provided sub domain analysis and showed that on at least one measure 10% or less or the sample scored in the "normal" ranges. This supports the possibility that cognitive deficits occur in certain sub-domains but not all—particular appropriate for measures of motor and mental development. IQ (general, practical and verbal) was found to be affected in children who have neuroimaging abnormalities. There is a notable absence of information for the youngest age ranges.

5. Conclusion

Despite the shortcomings of the data, the challenges in synthesising the studies and the broad umbrella of concepts included under the heading of cognitive and behavioural performance, this updated review shows clear on-going evidence that children with HIV may well have special educational needs and face the prospect of cognitive delay in some domains of functioning. These results are now well established and they suggest that centres should be considering routine cognitive monitoring for children from an early age and on a regular basis and the provision of interventions to ameliorate or cater for the cognitive function needs of children. Early child development and stimulation may be particularly relevant for young children, despite the paucity of data for the youngest age groups. For older children, school provision and adaptations for special needs requirements should be prioritised to accommodate their needs. Future studies ought to untangle the complex potential causal chains and pathways which contribute to the findings. Well validated scales and agreed measures are overdue. Intervention studies are urgently needed and learning from the non HIV child developmental delay literature should serve to inform possible remedial or supportive provision, treatment decisions, compound choices and special educational provision to overcome or accommodate such cognitive delay.

Appendix A

A.1. PsycINFO search

1. Exp HIV/(27361)
2. (HIV or human immunodeficiency syndrome or AIDS or acquired immunodeficiency virus).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (47730)
3. 2 or 4 (42483)
4. (child or minor or infant or preteen or baby or newborn or neonate).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (195748)
5. exp Early Childhood Development/(17861)
6. exp Infant Development/(11423)
7. exp Cognitive Development/(28953)
8. exp Cognitive Ability/(48562)
9. exp Cognitive Impairment/(18708)
10. (cognitive development or development or neurological functioning or intellectual or learning or language or memory).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (670258)
11. exp AIDS Dementia Complex/(120)
12. (child behaviour or child behavior).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (12024)
13. exp Psychosocial Development/(18755)
14. exp Emotional Development/(3973)
15. exp Physical Development/(18931)
16. (social development or physical development or emotional development).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (10074)
17. 9 or 11 or 13 or 15 or 17 or 19 or 21 or 23 or 25 or 27 or 29 or 31 or 33 (713624)
18. (control or comparison).mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (298776)
19. comparative.mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (25922)
20. exp Experiment Controls/(405)
21. exp Intervention/(46460)
22. (intervention or time-series or case-control or "before and after").mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (153646)
23. 36 or 38 or 40 or 42 or 44 (437797)
24. 5 and 7 and 34 and 45 (322)

A.2. Medline search

1. HIV infections/(127971)
2. (HIV or human immunodeficiency virus or AIDS or acquired immunodeficiency virus).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (284755)
3. 2 or 4 (284755)
4. Child/(744764)
5. Infant/(332968)
6. (child or minor or infant or preteen or baby or newborn or neonate).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1344606)
7. 7 or 9 or 11 (1344606)
8. Delirium, Dementia, Amnestic, Cognitive Disorders/(3312)
9. (cognitive development or development or neurological functioning or intellectual or learning or language or memory).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1400887)
10. (child behaviour or child behavior).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (18334)
11. (social development or physical development or emotional development).mp. [mp = title, abstract, original title, name of

substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (3277)
12. Child Development/(18348)
13. 14 or 16 or 18 or 20 or 22 (1415171)
14. Control Groups/(1199)
15. Comparative Effectiveness Research/(904)
16. Intervention Studies/(5598)
17. (intervention or time series or case-control or "before and after").mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (570287)
18. (control or comparison).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1898112)
19. comparative.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1232605)
20. 25 or 27 or 29 or 31 or 33 or 35 (3036475)
21. 5 and 12 and 23 and 36 (1417)

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