Published in final edited form as:

AIDS Care. 2019 March ; 31(3): 275–282. doi:10.1080/09540121.2018.1533629.

Interventions for Developmental Delays in Children Born to HIV-infected Mothers: A Systematic Review

Megan Song McHenry, MD, MS,
Indiana University School of Medicine, Department of Pediatrics, Indianapolis, Indiana, USA, Telephone: +1-317-278-0552, msuhl@iu.edu

Carole Ian McAteer, MPH,
Indiana University School of Medicine, Department of Pediatrics, Indianapolis, Indiana, USA, Telephone: +1-317-287-6882, carolemcateer@gmail.com

Eren Oyungu, MBChB, MMED,
Moi University, College of Health Sciences, School of Medicine, Department of Child Health and Paediatrics, Eldoret, Kenya, Telephone: +254 722 344 312, erenoyungu2002@yahoo.co.uk

Andrew Roland Deathe, and
Indiana University School of Medicine, Department of Pediatrics, Indianapolis, Indiana, USA, Emory University, Rollins School of Public Health, Atlanta, Georgia, USA, Telephone: +1-260-393-5277, ardeathe@iu.edu

Rachel Christine Vreeman, MD, MS
Indiana University School of Medicine, Department of Pediatrics, Indianapolis, Indiana, USA, Telephone: +1-317-287-6882, rvreeman@iu.edu

Abstract

Children born to HIV-infected mothers have worse developmental outcomes compared to HIV-unexposed children. However, little is known about interventions to improve developmental outcomes in this population. This study systematically reviews the literature on interventions to improve development in children born to HIV-infected mothers. We systematically searched the following electronic bibliographic databases: Ovid MEDLINE, Embase, PsycINFO, Education Resources Information Center, and the Cochrane Database of Systematic Reviews. Studies were selected on the basis of defined inclusion criteria and excluded if antiretroviral medication was the only intervention. Titles, abstracts, and full texts were assessed by 2 independent reviewers. Data were collected on characteristics of the study design, intervention, and developmental outcomes measured. Risk of bias and strength of evidence were assessed on all included articles. Our search resulted in 11,218 records. After our initial review, 43 records were appraised in their entirety and 9 studies met all inclusion criteria. Six were performed in sub-Saharan Africa, while the remaining 3 were performed in the United States. Eight were randomized-controlled trials and one was a

Corresponding Author: Megan McHenry, MD, MS, Assistant Professor of Pediatrics, Ryan White Center for Infectious Diseases and Global Health, Department of Pediatrics, Indiana University School of Medicine, 410 W. 10th Street, HITS Suite 2000V, Indianapolis, IN, 46202, msuhl@iu.edu, Telephone: 317-278-0552, Fax: 317-278-0456.

Financial Disclosure Statement: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest Statement: The authors have no conflicts of interest relevant to this article to disclose.

retrospective chart review. Four studies focused on caregiver-training, 2 studied massage therapy, and the remaining studies focused on maternal vitamin supplementation, video-based cognitive therapy, or center-based interventions. Massage therapy had the most consistent improvements in the domains measured, while caregiver training and cognitive therapy interventions had limited benefits. The center-based intervention showed no benefit. Only 3 studies had a low risk of bias, and 4 studies had good strength of evidence. Most studies found some benefit. However, these findings are limited by the quality of the study designs, small sample size, and heterogeneity of the interventions and assessments used to measure outcomes. There is a critical need for the creation of evidence-based interventions to promote development in this vulnerable population.

Keywords

HIV; pediatrics; intervention; child development; developmental delays

Introduction:

Children born to HIV-infected mothers have worse developmental outcomes compared to their unexposed peers (Abubakar, Van Baar, Van de Vijver, Holding, & Newton, 2008; McHenry et al., 2018; Phillips et al., 2016; Sherr, Croome, Parra Castaneda, Bradshaw, & Romero, 2014). Both cognitive and motor development are negatively impacted in young HIV-infected and -exposed children (McHenry et al., 2018). For older children and adolescents, working memory, processing speed, and executive function appear to be most affected (Phillips et al., 2016). While research is ongoing to determine the etiology of these delays, the 1.5 million children born to HIV-infected mothers each year continue to be at risk for poor development (United Nations Children's Fund, 2013).

In the age of expanding coverage of antiretroviral medication, these children have the ability to live long, healthy lives. While antiretroviral medications alone improve neurodevelopmental outcomes in HIV-infected infants (Laughton et al., 2012) and adolescents (Gomez et al., 2018), these children continue to have lower developmental and cognitive scores compared to their uninfected peers (Nozyce et al., 2006). If HIV-infected and –exposed children are unable to reach their full developmental potential, their quality of life, academic achievement, and economic potential may be negatively impacted (Chilton, Chyatte, & Breaux, 2007; Grantham-McGregor et al., 2007). Thus, it is critical that interventions are implemented that can lessen or reverse these negative effects.

Intervening early in childhood for developmental delays, particularly within the first three years of a child's life, is known to have the greatest potential for benefit, due to the dynamic changes in brain plasticity in early life (Black et al., 2007; Guralnick & Bricker, 1987). However, little is known about interventions designed to address developmental delays in children born to HIV-infected mothers. While early interventions have been well-studied for the general population, they may not address the biological and social conditions that result from being born to an HIV-infected mother. Only one prior review has been conducted on interventions for cognitive delays in HIV- infected and -affected children, and despite the authors' strong methodologies, they found only 4 studies on this topic (Sherr, Croome,

Bradshaw, & Parra Castaneda, 2014). By broadening criteria to include other domains of development and performing an updated review, we hope to gain greater perspectives on developmental interventions for this population. The objective of this study is to review the current literature on interventions for developmental delays in children born to HIV-infected mothers.

Methods:

The Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) Protocols 2015 Checklist was used when conducting this systematic review and meta-analysis (Moher, Liberati, Tetzlaff, Altman, & The Prisma Group, 2009).

Search Strategy:

We conducted a systematic search using a protocol designed by a medical librarian specifically for this study (Table 1) in 4 electronic databases: Ovid MEDLINE, PsycINFO, Embase, and Education Resources Information Center. We also searched Google Scholar, Cochrane Database for Systematic Reviews, and the bibliographies of pertinent articles. The search encompassed articles published from January 1, 1990 to December 15, 2017. The initial screening was performed by 2 independent reviewers (MM and CM), who assessed the titles and abstracts from the search. Records were managed using the citation managing program, Endnote X7™. From this initial screen, articles were immediately excluded if they did not study an intervention for developmental delays in HIV-infected or exposed children <18 years of age or if it was a review article. After the initial exclusion process, two authors (MM and CM) independently reviewed the full text of the remaining articles to determine whether articles met the predetermined eligibility criteria. Disagreements between the 2 reviewers regarding the inclusion or exclusion of particular studies were settled by consultation with a third reviewer (RV).

Eligibility:

The following inclusion criteria were applied: (1) have either a HIV-infected or –exposed population; (2) only include children <18 years of age; (3) have an intervention; (4) use a standardized neuropsychological instrument with reported results. Studies were excluded if their entire population had a significant confounding factor, such as hemophilia or congenital cytomegalovirus infection. Studies were also excluded if the only intervention was antiretroviral therapy. Review articles, published abstracts without full-text publications, and case study reports containing <10 participants were excluded. Although our search strategy specified English language articles, a few non-English articles were included in our initial search results and they were included for evaluation. We did not exclude published theses that otherwise met inclusion criteria.

Data Extraction:

Two reviewers independently extracted data from the manuscripts into an electronic table. All extracted data were then cross-checked independently by one other reviewer. The following variables were extracted from the studies: study population (age, HIV status,

antiretroviral medication exposure, country, and sample size), study design, description of the intervention, comparison group used, outcomes measured, and results.

Quality Assessment:

Quality was assessed using two methodologies in this study: Risk of Bias and Strength of Evidence. The Risk of Bias Tool was developed by the Cochrane Collaboration to provide a clearer and more accurate process for assessing risk of bias for randomized trial designs (Higgins et al., 2011). The Strength of Evidence Tool was developed to help assess study quality for various study types, included controlled intervention studies, observational cohorts, and cross-sectional studies (National Heart Lung and Blood Institute). The two reviewers independently rated each article on Risk of Bias and Strength of Evidence. Any disagreements were settled after discussion and by consensus.

Results:

Our search resulted in 11,218 records. After our initial review of all records, 43 records were appraised in their entirety. Of the 43 records, 9 studies met all inclusion criteria (Figure 1). Six were performed in sub-Saharan Africa (3 in Uganda, 2 in South Africa, and 1 in Tanzania), while the remaining 3 were performed in the United States. Eight were randomized-controlled trials, and one was a retrospective chart review. Three studies indicated that a proportion of the study participants was on antiretroviral treatment, 1 study reported that participants received perinatal antiretroviral prophylaxis, 1 study noted that antiretroviral medications were not available during the study period, and the remaining 4 studies did not mention antiretroviral medications. Only 3 studies had a low risk of bias, and 4 studies had good strength of evidence (Table 2; Supplemental Table 1).

Caregiver-Training Interventions

Four studies focused on caregiver-training interventions. Caregiver-training interventions are parenting programs administered directly to parents or caregivers of young children, by trained facilitators, to improve relationships and interactions between caregivers and their children to promote positive development. Two studies used the same caregiver-training program in Uganda: the Mediational Intervention for Sensitizing Caregivers (MISC) within a one year program (Boivin et al., 2013a, 2013b) for children roughly between the ages of 15–60 months. This bi-weekly intervention included field team-led training on health and nutrition of their children, as well as video-taped interactions which were reviewed with the caregivers to teach practical strategies for positively interacting with their children. For the study focused on HIV-infected children, scores for visual reception and immediate recall were significantly higher in the intervention group compared to the control ($p=0.014$ and $p=0.024$, respectively) (Boivin et al., 2013a). The scores on parent-child interactions, from video coding and home environment observations, improved significantly in the intervention group compared to the control (HOME: $p=0.029$; OMI: $p<0.001$). No differences were found in other domains of the developmental assessments, behavioral assessments, or caregiver anxiety. Caregiver depression scores were improved in the intervention group at 6 months but were not significantly different from the control group at 12 months (Boivin et al., 2013a). In the complementary study of HIV-exposed but uninfected children in Uganda

randomized to the same intervention and controls, the results were fairly similar (Boivin et al., 2013b). The intervention group had gains over the controls in more domains than in the study focused on HIV-infected children, with improvements in receptive language ($p=0.004$), expressive language ($p=0.001$), and the composite score of overall cognitive ability ($p=0.006$). The intervention group also had improvements in scores of parent-child interactions, from video coding and home environment observations ($p<0.001$ for both) (Boivin et al., 2013b).

One study from the United States used a parenting intervention delivered by community health nurses within the homes of infants born to HIV-infected mothers for the first 18 months of life (Black, Nair, & Harrington, 1994). While there was some improvement in certain subscales of the home observations and screening for child abuse potential, there were no other differences in child development scores, parenting stress, family support and adaptability, or parent-child relations (Black et al., 1994).

In South Africa, a qualified physiotherapist designed a home stimulation program for young (less than 30 months old) HIV-infected children that was discussed and updated during clinic visits but intended to be delivered by parents within the home (Potterton, Stewart, Cooper, & Becker, 2010). The degree of improvement of cognitive and motor scores was significantly higher in the intervention group ($p=0.01$ and $p=0.02$, respectively) (Potterton et al., 2010). However, the authors note that the mean cognitive and motor scores for all children at the end of the study indicated that a large number of the children had persistent developmental delays (Potterton et al., 2010).

Massage Therapy

Two studies focused on massage therapy. One study in the United States only performed the intervention on neonates born to HIV-infected mothers for the first 10 days after birth (Scafidi & Field, 1996). The authors found that the intervention group scored higher compared to the control group in multiple sub-scales of the Brazelton neonatal assessment, including habituation ($p=0.01$), motor ($p=0.001$), range of state ($p=0.05$), autonomic stability scores ($p=0.003$), excitability ($p=0.01$), and stress behaviors ($p=0.004$) (Scafidi & Field, 1996). The second study focused on infants born to HIV-infected mothers in South Africa and trained mothers to perform massage therapy daily to their infants between 6 weeks and 9 months of life (Perez et al., 2015). While the intervention group had higher scores in all sub-scales of the Griffiths Mental Development Scales, statistically significant differences were only found in the hearing and speech quotient (21.9 vs 11.2, $p<0.03$) and the general quotient (19.3 vs 7.7, $p=0.03$) (Perez et al., 2015). Neither study looked at follow-up beyond 9 months of life.

Maternal Vitamin Supplementation

One study included in the review focused on vitamin supplementation in mothers. This was a secondary analysis of a large randomized controlled trial using multivitamins and vitamin A in pregnant and postpartum HIV-infected mothers in a 2×2 factorial design in Tanzania where children were followed for 18 months (McGrath et al., 2006). There was a small increase in the motor scores in the multivitamin group compared to the control group over

time (p=0.04), and multivitamins were found to be protective again the risk of motor delays (relative risk: 0.4; 95%CI: 0.2–0.7). No differences were found in the vitamin A group or when evaluating cognitive ability (McGrath et al., 2006).

Video-based Cognitive Therapy

One study from Uganda looked at cognitive rehabilitation using a computer game with school-aged children infected with HIV (Boivin et al., 2010). The intervention group had twice weekly sessions in clinic for a period of five weeks, and the Cosgate neuropsychological battery of six sub-tests were used for assessments at baseline and after 5 weeks of intervention (Boivin et al., 2010). Compared to the control group, the intervention group had improved scores in two sub-tests: maze learning ($p<0.001$) and detection speed ($p=0.02$) (Boivin et al., 2010).

Center-based Intervention

One retrospective study looked at the impact a center-based intervention had on cognitive development in children born to HIV-infected mothers in the United States using a pre- and post- intervention analysis (Dedomenico, 1999). The intervention was an entry evaluation to determine eligibility for early intervention services, as well as referral to those services within the community center (Dedomenico, 1999). The study found that the HIV-exposed children had lower scores at baseline compared with HIV-infected children, but after adjusting for gestational age, there were no significant differences in either cognitive or motor outcomes after two years for either group (Dedomenico, 1999).

Discussion:

This systematic review highlights the persistent challenges surrounding the limited data describing interventions to address delays in development in children born to HIV-infected mothers. We found interventions focused on caregiver training, massage therapy, cognitive therapy, and center-based care. Tools used to assess parent-child interactions and development varied widely among the studies. Massage therapy had the most consistent improvements in the domains measured, while caregiver training and cognitive therapy interventions showed some benefit. The center-based intervention did not show benefit.

Currently, it is unclear why children born to HIV-infected mothers may be at higher risk for developmental delays. While HIV-infected children do benefit from antiretroviral treatment in multiple ways, including in their development, delays continue to exist when treatment is started later in infancy and life (Gomez et al., 2018; Laughton et al., 2012). Both HIV-infected and –exposed children have been found to have differences in their brain structure and function, which is associated with lower cognitive functioning in some studies (Jankiewicz et al., 2017; Keller et al., 2004; Tran et al., 2016; Yadav et al., 2017). These changes could potentially be due to effects of *in utero* HIV or antiretroviral medication exposure, increased rates of maternal depression in HIV-infected mothers, increased rates of poverty, increased physiological stress related to being born in a household affected by HIV, or, what may be more likely, a combination of these factors and more. However, until more is known about the reason for increased delays, the best way of approaching developmental

interventions for children born to HIV-infected mothers may be to consider effective developmental interventions being used in the general population.

Most interventions within this review used a caregiver-training program. While two of the studies looked at the same program, MISC, the others looked at different programs, administered by different types of providers with varying methodologies for the studies' specific target populations, resulting in considerable heterogeneity within this category. While these programs had moderate benefits in the domains measured, other caregiver training programs have shown great benefit in populations that are not exposed to or infected with HIV. UNICEF's Care for Child Development, an internationally recognized caregiver program, has been showed to improve cognitive, language, and motor outcomes at 12 and 24 months of age in Bangladesh (Yousafzai, Rasheed, Rizvi, Armstrong, & Bhutta, 2014). The caregiver trainings were conducted by community health workers during monthly home visits until 24 months of age (Yousafzai et al., 2014). To our knowledge, no studies have been published using Care for Child Development for children born to HIV-infected mothers. It would be critical to know whether differences exist between programs such as the MISC and Care for Child Development, possibly in their curriculum, the manner in which they are delivered, or their target populations, which may result in one program having more benefits over another. Currently, the heterogeneity of the programs within this intervention category limits our ability to compare caregiver-training programs at this time.

In our review, massage therapy had the most consistent evidence of developmental benefit for infants of HIV-infected mothers, and both studies had good quality of evidence to support these results (Perez et al., 2015; Scafidi & Field, 1996). While these studies only followed the children for a short time, other research suggests that massage therapy in high-risk infants may have positive impacts on development into toddlerhood. In one study, very low birth weight infants receiving massage therapy had improved cognitive scores and had borderline improved motor scores at two years of age compared to those without massage therapy (Procianoy, Mendes, & Silveira, 2010). A Cochrane review on this topic revealed limited evidence of benefit for low-risk groups of parents and infants; however, more research is needed to determine the impact of infant massage in higher-risk groups, such as children born to HIV-infected mothers (Bennett, Underdown, & Barlow, 2013).

The connection between micronutrient deficiencies and cognitive development have been well-studied in the general population (Grantham-McGregor & Ani, 1999; Walker et al., 2007). Maternal or infant micronutrient supplementation appears to have some benefit to infants that would otherwise be nutritionally at risk, especially folate for preventing neural tube defects and vitamin A for reducing mortality and diarrhea (McHenry, Dixit, & Vreeman, 2015; Vaivada, Gaffey, & Bhutta, 2017). However, while there may be some benefits of nutritional supplementation specific to developmental delays, data specific to children born to HIV-infected mothers was limited to the one study included in our review (McGrath et al., 2006). More research is needed to determine if nutritional supplementation could improve developmental outcomes for HIV-infected and -exposed children.

While this review did include one study on center-based intervention, it did not contain large-scale programmatic interventions, such as preschool and early childhood education

programs which address early cognitive skills on a larger scale. In the United States, high-quality programs providing early intervention like Head Start and the Carolina Abecedarian Project have been found to increase IQ scores, retain children in school, and reduce subsequent placement in special education courses (Campbell & Ramey, 1994, 1995; Schanzenbach & Bauer, 2016; Zigler, Abelson, Trickett, & Seitz, 1982). A possible reason for the lack of studies on programmatic interventions is that such studies generally focus on evaluating a population-based sample to capture greater numbers of children at-risk for poor development, rather than focusing primarily on one group of children. Another potential concern in the resource-limited settings where HIV is most prevalent is that many early childhood education programs require considerable spending per child in order to maintain high quality. For example, Head Start costs approximately $7,222 per child per year (Besharov, Myers, & Morrow, 2007). While these costs are offset by reduced need for special education resources and the improved economic potential of the children, the financial and logistic resources required to implement such programs are great, and only a few resource-limited countries have been able to do this successfully with high-quality programming (Darmstadt, 2017; Richter et al., 2017; Veronica Silva V). Low-quality programs -- those with large numbers of children per instructor and with limited training for instructors in early childhood education -- do not show the same benefits for cognitive development that high-quality programs do (Frede, 1995). As more countries push for early childhood programs, it is critical that high quality standards are maintained so that limited resources are used in the most effective manner to promote early childhood development for at-risk children.

The results of this review have some limitations. First, the risk of bias and strength of evidence evaluations revealed that most studies included in this review did not contain high-quality evidence supporting their results. Many of the articles were published prior to the creation of quality guidelines (Higgins et al., 2011). Some of these older studies may be able to provide stronger evidence, however, we assessed the studies solely on the authors' descriptions within their publications. Most studies included in this review were not powered to find differences between intervention and control groups, and thus, small sample size was a limitation. Additionally, there was significant heterogeneity among the interventions and assessments used to measure outcomes, which makes interpretation of the results challenging. Further consensus is needed to determine which outcomes are most meaningful to measure.

While our review found that massage therapy, caregiver-training, and cognitive therapy had some benefits to children born to HIV-infected mothers, the evidence is not strong enough to recommend a particular intervention for developmental delays in this population at this time. More research is needed to determine effective, culturally appropriate interventions to address developmental delays in children born to HIV-infected mothers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgements: The authors would like to thank Elizabeth Whipple, MLS for her help in developing the search strategy used within this systematic review.

Funding source: Dr. McHenry's time was supported in part by a training grant entitled "Training in STIs and Other Infections of Global Health Significance" (T32AI007637, PI: Dr. Wools Kaloustian) from the National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

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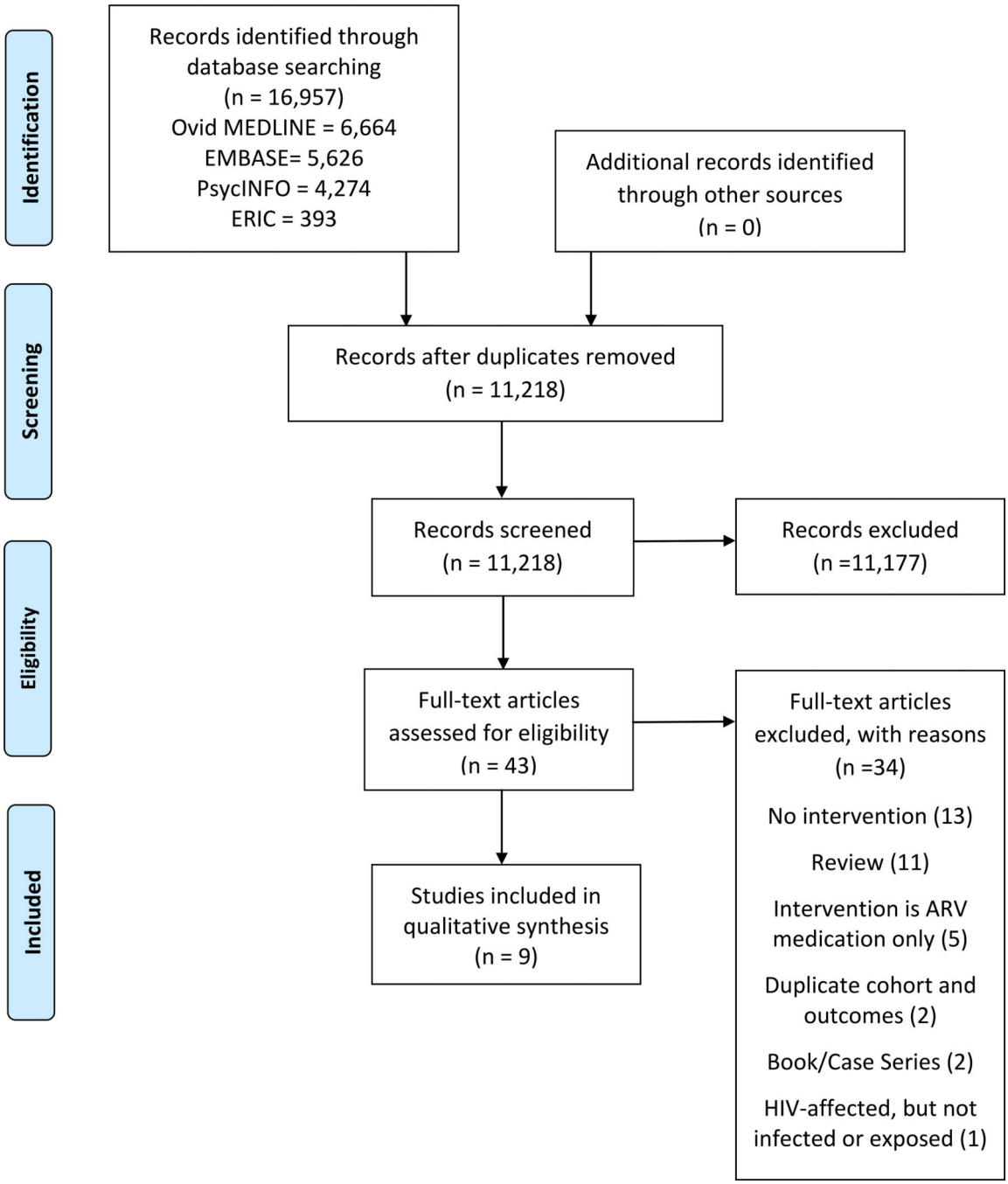

Figure 1:
PRISMA Flow Chart

Table 1:

Sample Search Strategy: Ovid Medline

OVID Search (Run on 12/15/2017)
1. neurodevelopment.mp. or exp Child Development/
2. development.mp. or exp Child Development Disorders, Pervasive/ or exp “Growth and Development”/ or exp Language Development/ or exp Human Development/ or exp Language Development Disorders/
3. exp Communication Disorders/ or exp Social Communication Disorder/ or exp Communication/ or communication.mp.
4. developmental disabilities.mp. or exp Developmental Disabilities/
5. exp Child Development Disorders, Pervasive/ or exp Autistic Disorder/ or developmental disorders.mp.
6. exp Intellectual Disability/ or developmental delays.mp.
7. child development.mp
8. neurodevelopmental disorders.mp. or exp Neurodevelopmental Disorders/
9. neurodevelopmental disabilities.mp.
10. neurodevelopmental delays.mp.
11. exp Psychomotor Disorders/ or exp Motor Skills Disorders/ or exp Motor Skills/ or developmental coordination.mp. or exp Psychomotor Performance/
12. cognition disorder.mp. or exp Cognition Disorders/
13. social behavior disorder.mp. or exp Social Behavior Disorders/
14. cerebral palsy.mp. or exp Cerebral Palsy/
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp HIV/ or HIV.mp. or exp HIV-2/ or exp HIV-1/
17. acquired immunodeficiency syndrome.mp. or exp Acquired Immunodeficiency Syndrome/
18. exp Anti-HIV Agents/
19. 16 or 17 or 18
20. 15 and 19
21. limit 20 to (yr=“1990 -Current” and (“all infant (birth to 23 months)” or “all child (0 to 18 years)” or “newborn infant (birth to 1 month)” or “infant (1 to 23 months)” or “preschool child (2 to 5 years)” or “child (6 to 12 years)” or “adolescent (13 to 18 years)” and English)

Table 2:

Study Characteristics

						Intervention									
Author (year)	**Country**	**Study Design**	**Sample size**	**Ages**	**Antiretroviral medication exposure**	**Description**	**Duration/ Intervals**	**Administrator of Intervention**	**Target of Intervention**	**Comparison**	**Outcomes Measured**	**Intervals of outcomes measured:**	**Results**	**Risk of bias**	**Strength of Evidence**
Black, et al (1994) (study 1)	USA	RCT	Total N = 60 children born to HIV-infected mothers Intervention: *n* = 31 Control: *n* = 29	Birth - 30 months	Information not reported	The in-home intervention had 4 objectives: 1) forming therapeutic alliance with mother 2) support mother's environment/ personal/fam needs 3) provide opportunities to enhance parent-child interaction and development 4) Provide information about child care, safety, and community resources	Two visits prior to birth and then bi-weekly visits after birth for first 18 months of life	Community health nurse	Mothers	No home visits or intervention	**Child:** Bayley Scales of Infant and Toddler Development (BSID) **Mothers:** Parenting Stress Index (PSI) Child Abuse Potential Inventory (CAPI) Family Support Scales (FSS) Family Adaptability and Cohesion Evaluation Scale (FACES-III) Parent Child Early Relational Assessment (PCERA) Home Observation for Measurement of the Environment (HOME)	BSID was performed at 6, 12, 18 months of age PSI was performed at 3 and 18 months of age CAPI was performed during the prenatal period and at 18 months of age FSS was performed during the prenatal period FACES-III was performed during the prenatal period PCERA was performed at 9 months of age HOME was performed at 30 months of age	The intervention group had significant higher HOME scores on two of the six subscales: (a) emotional and verbal responsivity of the mother and (b)opportunities for variety in daily stimulation. There were no differences related to HIV status. HIV+ women in intervention had more normative scores on the CAPI compared to HIV+ women in control group. No other differences in PSI, BSID, FSS, FACES-III, or PCERA were seen between the intervention and control groups, regardless of HIV status.	High	Poor
Boivin, et al (2010)	Uganda	RCT	Total N = 60 HIV+ children Intervention: *n* = 32 Control: *n* = 28	6–16 years	*n* = 13 (41%) of the children in the intervention group and *n* = 10 (36%) of children in the control group received Trimune (lamivudine, stavudine, and nevirapine). No information regarding perinatal medication exposure was included	Captain's Log Computerized Cognitive Rehabilitation Therapy (CCRT): Out of the possible 35 multi-level brain-training exercises for cognitive skills, 4 attention exercise, 4	10 sessions: twice weekly for 5 weeks	The CCRT was self-administered in the clinic	Children	No cognitive intervention	Cosgate neuropsychological battery: maze chasing, maze learning, detection speed, identification speed, one card learning, working memory.	Baseline and after 5 weeks	In an adjusted analysis, maze learning and detection speed improved in the intervention group compared to the control group ($p < 0.001$ and $p=0.02$, respectively).	Unclear	Fair-Poor

						Intervention									
Author (year)	**Country**	**Study Design**	**Sample size**	**Ages**	**Antiretroviral medication exposure**	**Description**	**Duration/ Intervals**	**Administrator of Intervention**	**Target of Intervention**	**Comparison**	**Outcomes Measured**	**Intervals of outcomes measured:**	**Results**	**Risk of bias**	**Strength of Evidence**
						conceptual / memory exercises, 3 visual motor exercises, and 4 logic module exercises were used for the intervention.									
Boivin, et al (2013a)	Uganda	RCT	Total N = 120 HIV+ children Intervention: *n* = 60 Control: *n* = 60	16 months – 5 years	One-half of the children in the intervention group and 57.8 % of the control children were on treatment during the intervention year. This treatment was Trimune (lamivudine, stavudine, and nevirapine). No information regarding perinatal medication exposure was included	Meditational Intervention for Sensitizing Caregivers (MISC)- teaches caregivers practical strategies for 1) focusing; 2) exciting; 3) expanding; 4) encouraging; 5) regulating	Bi-weekly training on health and nutrition for mothers/ caregivers, including videotaping of caregiver bathing, feeding, and working with the child. These videos tapes were reviewed during the bi-weekly trainings.	MISC field team workers (trained by MISC consultants)	Caregivers	No training	**Child:** Mullen Early Learning Scales (MELS) Color-Object Association Test (COAT) **Caregiver:** Achenbach Child Behavior Checklist (CBCL) Hopkins Symptoms Checklist (HSCL) Home Observation for Measurement of the Environment (HOME) Observing Medication Interactions (OMI)	Baseline, 6 months, and 1 year	MELS: The MISC group had a higher baseline scores for visual reception, expressive and receptive language compared to the controls. When adjusted, the rate of improvement between the MISC group and controls was only seen for visual reception. (p=0.014) COAT: The MISC group had significantly group-by-time effect compared to the control group for immediate recall (p=0.024), but not significant for total memory CBCL: No difference HSCL: MISC caregivers less depressed on HSCL at 6 months than control caregivers but not significant at 12 months. No difference with HSCL anxiety. HOME and OMI: MISC group had significant group-by-time	Unclear	Fair-Poor

						Intervention									
Author (year)	**Country**	**Study Design**	**Sample size**	**Ages**	**Antiretroviral medication exposure**	**Description**	**Duration/ Intervals**	**Administrator of Intervention**	**Target of Intervention**	**Comparison**	**Outcomes Measured**	**Intervals of outcomes measured:**	**Results**	**Risk of bias**	**Strength of Evidence**
													effect compared to the control group. (HOME: p=0.029; OMI: p<0.001)		
Boivin, et al (2013b)	Uganda	RCT	Total N = 119 HEU children Intervention: *n* = 60 Control: *n* = 59	2 – 4 years of age	Information not reported	Meditational Intervention for Sensitizing Caregivers (MISC)- teaches caregivers practical strategies for 1) focusing; 2) exciting; 3) expanding; 4) encouraging; 5) regulating	Bi-weekly training on health and nutrition for mothers/ caregivers, including videotaping of caregiver bathing, feeding, and working with the child. These videos tapes were reviewed during the bi-weekly trainings.	MISC field team workers (trained by MISC consultants)	Caregivers	No training	**Child:** Mullen Early Learning Scales (MELS) Color-Object Association Test (COAT) **Caregiver:** Achenbach Child Behavior Checklist (CBCL) Hopkins Symptoms Checklist (HSCL) Home Observation for Measurement of the Environment (HOME) Observing Medication Interactions (OMI)	Baseline, 6 months, and 1 year	MELS: The MISC group had greater gains over time compared to controls in receptive language (p=0.004), expressive language (p=0.001), and the composite score of overall cognitive ability (p=0.006). COAT: The MISC group showed more improvement than controls, it was not statistically significant. CBCL: No differences were noted HSCL: Both the MISC and control groups had improvement of scores over time, without significant differences between the groups. HOME and OMI: The MISC groups had significant improvement of scores compared to control (p<0.0001).	Unclear	Fair-Poor
Dedomenico, et al (1999)	USA	Retrospective Chart Review	N = 75 children in ICLC born to HIV-infected mothers HIV+ children: *n* = 36 HIV- children: *n* = 39	0 months - 66 months	Information not reported	Infant and Child Learning Center (ICLC): Integrated inpatient hospital services with a community-based early	At least 2 years of being in ICLC (year 1 developmental assessments done, year 2 developmental assessments done)	Healthcare professionals	Children	N/A	BSID: Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) McCarthy Scale of Children's Abilities (MSCA)	At entry into the program, after 1 year of ICLC, after 2 years of ICLC	The HIV-negative group initially had lower cognitive and motor scores compared to the HIV-positive group. After adjusting for gestational	N/A	N/A

						Intervention									
Author (year)	**Country**	**Study Design**	**Sample size**	**Ages**	**Antiretroviral medication exposure**	**Description**	**Duration/ Intervals**	**Administrator of Intervention**	**Target of Intervention**	**Comparison**	**Outcomes Measured**	**Intervals of outcomes measured:**	**Results**	**Risk of bias**	**Strength of Evidence**
						intervention program. Services such as special education, occupational, physical, speech and language therapy are available.					Stanford Binet 4th Edition		age, there were not significant differences in cognitive or motor outcomes over time.		
McGrath, et al (2006)	Tanzania	A secondary analysis on data from an RCT using multivitamins and vitamin A in a 2×2 factorial design	N = 327 children born to HIV+ mothers No multivitamin: *n* = 158 Multivitamins: *n* = 169 No Vitamin A: *n* = 147 Vitamin A: *n* = 180	6 – 18 months	Authors note that treatment was not available to the majority of Tanzanians during the time of this study.	Mothers received either vitamin A, multivitamin excluding vitamin A, multivitamin including vitamin A, or placebo. All children born to mothers in the initial RCT, regardless of the maternal vitamin regimen, received vitamin A (100,000 IU) at 6 months of age and a double dose (200,000) every 6 months.	Mothers between 12–27 weeks pregnant and 18 months post Women received daily doses during pregnancy (starting between 12–27 weeks gestation) and continued after delivery. Children received vitamin A at 6 months of age and again at every 6 months after.	Nurses provided vitamins to mothers to consume.	Mothers	N/A	Bayley Scales of Infant Development, 2nd edition (BSID-II), (MDI and PDI)	6, 12, and 18 months.	Receiving multivitamins was associated with a mean increase in motor scores of 2.6 points (p=0.04) over time and was found to be protective against the risk for developmental delay in the motor domain (relative risk: 0.4; 95%CI: 0.2–0.7). There were differences found with the mental development scale. Vitamin A had no significant effect on these outcomes.	Unclear	Good
Perez, et al (2015)	South Africa	RCT	Total N = 161 HIV-exposed Intervention: *n* = 73 Control: *n* = 88	6 weeks - 9 months	HIV-infected mothers received zidovudine during pregnancy. Nevirapine was given to HIV-infected mothers during labor and to the infant within 72 hours of delivery. HIV-exposed children were also given prophylaxis for *Pneumocystis jirovecii* pneumonia with cotrimoxazole for 6 weeks	Massage therapy-mothers trained to massage infants	Mothers who were trained to massage infants for 15 minutes daily	Massage therapist taught massage techniques to mothers	Mothers	No massage therapy training for mothers in control group	Griffiths Mental Development Scales Infant anthropometrics	6 weeks and 9 months	The intervention group had higher mean difference between 6 weeks and 9 months for all five domains of the Griffiths Scale compared to the control group, with statistically significant differences found in the hearing and speech quotient (21.9 vs 11.2, p<0.03) and the general quotient (19.3 vs 7.7, p=0.03).	Low	Good

						Intervention									
Author (year)	**Country**	**Study Design**	**Sample size**	**Ages**	**Antiretroviral medication exposure**	**Description**	**Duration/ Intervals**	**Administrator of Intervention**	**Target of Intervention**	**Comparison**	**Outcomes Measured**	**Intervals of outcomes measured:**	**Results**	**Risk of bias**	**Strength of Evidence**
													There were no significant differences in anthropometric measurements based on group or gender at 6 weeks or 9 months of age.		
Potterton, et al (2010)	South Africa	RCT	N = 122 HIV+ children Intervention: *n* = 60 Control: *n* = 62	< 2.5 years	During the course of the study, changes within South African government allowed more individuals to be on therapy. At baseline, n = 13.3% of the experimental group and 16.1% of the control group were on therapy. At 12 months, n = 86.1% of the experimental group and 85.7% of the control group were on therapy. There was no significant different between the two groups in terms of the number of therapy and the specific drug regimen was not identified.	Intervention group received individual home stimulation programmes which included activities to promote early childhood development.	Follow-up visits every 3 months where the individual home programme was updated	Research assistant (qualified physiotherapist) created home stimulation programmes	Caregivers	No home programme for children in the comparison group	BSID-II (MDI and PDI)	Baseline, 6, and 12 months	PDI: The degree of improvement over time was significantly greater in the intervention group (from PDI 49.8 to 70.5; compared to the control group (from PDI 57.4 to 65.9) (p=0.02). MDI: The degree of improvement over time was significantly greater in the intervention group (from MDI 62.6 to 69.3) compared to the control group (from MDI 68.5 to 64.3) (p=0.01). The mean PDI and MDI scores in all children at the end of the study period indicate that the children's development was still significant delayed.	Low	Good
Scafidi, et al (1996)	USA	RCT	N = 28 HIV-exposed neonates (number in each group not reported)	Neonates	Information not reported	Experimental group neonates received massage therapy post-delivery	Three 15-minute periods during 3 consecutive hours each day for 10-day period	Research assistant delivered the massage to the neonates	Neonates	Children who did not receive massage therapy	Brazelton neonatal assessment scale (habituation, orientation, motor behaviour, range of state, regulation of state, autonomic stability, abnormal reflexes)	Midway between feedings pre- and post- 10-day stimulation and massage period.	The massage therapy group scored better on habituation (p=0.01), motor (p=0.001), range of state (p=0.05), autonomic stability scores (p=0.003), excitability (p=0.01), and stress behaviors (p=0.004) after	Low	Good

						Intervention									
Author (year)	Country	Study Design	Sample size	Ages	Antiretroviral medication exposure	Description	Duration/ Intervals	Administrator of Intervention	Target of Intervention	Comparison	Outcomes Measured	Intervals of outcomes measured:	Results	Risk of bias	Strength of Evidence
													the 10 days compared to the control group. There was no difference in orientation, regulation of state, reflexes, or depression scores between groups over time.		