

# COGNITIVE AND MOTOR DEVELOPMENT IN HIV INFECTED CHILDREN: A SYSTEMATIC REVIEW

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*Thesis presented in partial fulfilment of the requirements for the degree of Masters of  
Nursing Science in the Faculty of Health Sciences at the University of Stellenbosch*



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## DECLARATION

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## **ABSTRACT**

The global epidemic of HIV continues with an estimated 2.2 million children under 15 years of age worldwide living with HIV and 640 000 newly infected in 2004 (WHO, 2009). HIV crosses the blood–brain barrier which may lead to neuronal damage and death. There is controversial evidence within available research on effects of HIV on cognitive and motor development in children because of the limitations imposed by study designs, study populations and study methodological quality.

The aims of the review were:

- To conduct a systematic review of published research to establish the effects and the prevalence of HIV infection on cognitive and motor development in children.
- To critically appraise the methodological quality of published research regarding cognitive and motor development of HIV infected children.

The objectives of the review were:

- To assess evidence on the cognitive and motor development of HIV-1 infected children
- To describe anthropometric outcomes including: weight for age, weight for height, height for age and head circumference in children with a HIV infection.
- To assess the methodological quality of studies on the cognitive and motor development of HIV infected children.

The following databases were searched for identification of articles; MEDLINE, Google Scholar, AIDSTRIALS, AIDSLINE and CINHALL. The search time frame included published works from inception to July 2011 without language restrictions.

Analytical observational trials that assessed at least one outcome (cognitive or motor development or 1 of the anthropometric outcomes) between HIV positive and HIV negative children aged 5 years and below or children with a mean age of less than 5 years were employed.

Two review authors independently searched for eligible studies, evaluated methodological quality and extracted the data. Meta-analysis was carried out using Rev Man 5.1 using the risk ratio for categorical data and standard mean difference for continuous data.

Fifteen studies with a total of 3 086 participants met the inclusion criteria. HIV infected children were 2.45 times at higher risk of developing cognitive developmental delay than HIV negative children (RR, 95% CI, 1.95, 3.07,  $P < 0.00001$ ). Infected children scored -0.54 less than HIV negative children (SMD 95% CI, -0.70, -0.39, 97,  $p < 0.00001$ ) for cognitive development and -0.68 in motor development (SMD 95% CI, -0.82, -0.55,  $p < 0.00001$ ). The risk of motor developmental delays was 2.95 times in HIV positive compared with HIV negative children (RR 95% CI, 2.19, 3.99,  $p < 0.00001$ ).

HIV infected children are slower in aspects of cognitive and motor development compared to their HIV negative counterparts. They also showed delays in anthropometric outcomes; weight for age and height for age. Study design influenced results of the studies with children scoring more on cross sectional than cohort studies. There is still need to develop culturally appropriate or standardise neurodevelopment tools as most African studies still rely on international tools. More evidence is needed on the effectiveness of HAART in reducing cognitive and motor delay.

## OPSOMMING

Die wêreldwye MIV epidemie duur voort met ongeveer 2.2 miljoen kinders onder 15 jarige ouderdom wat wêreldwyd met MIV leef en 640 000 onlangs in 2004 geïnfekteerd (WHO, 2009). MIV strek oor die bloed-brein grens wat kan lei tot neuronale skade en die dood. Daar is kontroversiële bewys binne beskikbare navorsing oor die effek wat MIV het op kognitiewe en motoriese ontwikkeling in kinders, vanweë die beperkinge wat geplaas word deur studie ontwerpe, studie bevolkings en studie metodologiese kwaliteit.

Die doelwitte van die oorsig is om

- 'n sistematiese oorsig van gepubliseerde navorsing te doen om sodoende die effek en voorkoms van MIV infeksie op kognitiewe en motoriese ontwikkeling by kinders vas te stel
- 'n kritiese waardering van die metodologiese kwaliteit van gepubliseerde navorsing te doen ten opsigte van die kognitiewe en motoriese ontwikkeling van MIV geïnfekteerde kinders.

Die doelwitte van die oorsig is om

- assessering te doen van die bewyse van kognitiewe en motoriese ontwikkeling by MIV-1 geïnfekteerde kinders
- antropometriese uitkomst te beskryf, insluitend: gewig vir ouderdom, gewig vir hoogte, hoogte vir ouderdom en omtrek van die hoof by kinders met 'n MIV infeksie
- die metodologiese kwaliteit te assesser van studies op die kognitiewe en motoriese ontwikkeling van MIV geïnfekteerde kinders.

Die volgende databasisse is nagevors vir die identifisering van artikels: MEDLINE, Google Scholar, AIDSTRIALS, AIDSLINE en CINHALL. Die tydraamwerk vir navorsing het gepubliseerde werk ingesluit vanaf aanvang tot Julie 2011 sonder taalbeperkings.

Analitiese waarneembare toetse wat ten minste een uitkoms geassesseer het (kognitiewe of motoriese ontwikkeling of 1 van die antropometriese uitkomst) tussen MIV positiewe en MIV negatiewe kinders van 5jarige ouderdom en jonger, of kinders met 'n gemiddelde ouderdom van minder as 5 jaar is betrek.

Twee oorsigouteurs het onafhanklik vir geskikte studies gesoek, metodologies geëvalueer en data getrek. Meta-analise was uitgevoer deur gebruik te maak van RevMan 5.1 met behulp van die risiko-ratio vir kategorieëse data en die standaard gemiddelde verskil vir aaneenlopende data.

Vyftien studies met 'n totaal van 3 086 deelnemers met die insluitingskriteria. MIV geïnfekteerde kinders het 2.45 keer 'n hoër risiko gehad om kognitiewe ontwikkelingsvertraging te ontwikkel as MIV negatiewe kinders (RR, 95% CI, 1.95, 3.07,  $P < 0.0000$ ). Geïnfekteerde kinders het 'n -0.54 telling behaal, minder as MIV negatiewe kinders (SMD 95% CI, -0.70, -0.39,  $p < 0.00001$ ) vir kognitiewe ontwikkeling en -0.68 vir motoriese ontwikkeling (SMD 95% CI, -0.82, -0.55,  $p < 0.00001$ ). Die risiko van motoriese ontwikkelingsvertraging was 2.95 keer by MIV positiewe in vergelyking met MIV negatiewe kinders (RR 95% CI, 2.19, 3.99.  $p < 0.00001$ ).

MIV geïnfekteerde kinders is stadiger in aspekte van kognitiewe en motoriese ontwikkeling in vergelyking met hulle MIV negatiewe eweknieë. Hulle het ook vertraging getoon in antropometriese uitkomst; gewig vir ouderdom en hoogte vir ouderdom. Studieontwerpe het uitslae beïnvloed van die kinders wat 'n hoër telling behaal het met deursnee as in kohort studies. Daar is nog 'n behoefte om kultureel geskikte of gestandaardiseerde neuro-ontwikkelingsinstrumente te ontwikkel, omdat die meeste Afrika-studies nog steeds staat maak op internasionale instrumente. Meer bewyse is nodig aangaande die effektiwiteit van HAART om kognitiewe en motoriese vertraging te verminder.

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## List of Abbreviations

AIDS:	Acquired Immune Deficiency Syndrome
ART:	Antiretroviral Therapy
AZT:	Zidovudine
BSID:	Bailey Scales of Infant Development
CENTRAL:	Cochrane Central Register of Controlled Trial
CINHAL:	Cumulative Index of Nursing and Allied Health
CAT:	Clinical Adaptive Test
CLAM:	Clinical Linguistic and Auditory Milestone Test
DDST:	Denver Developmental Screening Test
HAART:	Highly Active Anti-Retroviral Treatment
HIV:	Human Immunodeficiency Virus
KABC:	Kaufman Assessment Battery for Children
LTFU:	Loss to follow up
MDI:	Mental Development Index
MO:	Months
NOS:	New Castle for Observational Studies
PDI:	Psychomotor Development Index
PDMS:	Peabody Developmental Motor Scales
RevMan 5.1:	Review Manager (version 5.1)
RR:	Risk Ratio
SMD:	Standard Mean Difference
SON-R:	Snijders Oomen Nonverbal Intelligence Test–Revised
WPPSI-R:	Wechsler Preschool and Primary Scales of Intelligence-Revised

# **South African Journal of Psychology**

## **Information for Contributors**

### **Submission of a manuscript**

SAJP (South African Journal of Psychology) is a peer-reviewed journal publishing empirical, theoretical and review articles on all aspects of psychology. Articles may focus on South African, African or international issues. Manuscripts to be considered for publication should be e-mailed to [sajp@up.ac.za](mailto:sajp@up.ac.za). A covering letter with postal address, e-mail address and telephone number should be included. The covering letter should indicate that the manuscript has not been published elsewhere and is not under consideration for publication in another journal. An acknowledgement of receipt will be e-mailed to the author (within seven days, if possible) and the manuscript will be sent for review by three independent reviewers.

The manuscript number must always be quoted in ALL correspondence to the editor. Only one article per author will be published per calendar year. Exceptions to this rule will be at the sole discretion of the editor (with the associate editors) in the case of an exceptional article that needs to be published, a special issue where the specific article will make a significant contribution or a written response to a riposte, etc.

Where authors are invited to revise their manuscripts for re-submission, the editor must be notified (by e-mail) of the author's intention to resubmit and the revised manuscript re-submitted within six weeks. After a longer period, it will be treated as a completely new submission.

### **Manuscript structure**

Manuscripts (including references and tables) should be no longer than 20 pages (5 000 words), and must include the full title of the manuscript, the name(s) of the author(s) and her/his affiliations, and the name, postal address, and e-mail address of the corresponding author.

An abstract, no longer than 300 words, and an alphabetical list of at least six keywords should be provided. The introduction to the article does not require a heading. Tables and figures, with suitable headings/captions and numbered consecutively, should follow the reference list, with their approximate positions in the text indicated.

The manuscript should be an MS Word document in 12-point Times Roman font with 1.5 line spacing. The American Psychological Association (APA, ver. 5) style guidelines and referencing format should be adhered to.

### **Language**

Manuscripts should be written in English. It is compulsory that manuscripts be accompanied by a declaration that the language has been properly edited, together with the name and address of the person who undertook the language editing.

### **Ethics**

Authors should take great care to spell out the steps taken to facilitate ethical clearance, i.e. how they went about complying with all the ethical issues alluded to in their study, either directly or indirectly, including informed consent and permission to report the findings. If, for example, permission was not obtained from all respondents or participants, the authors should carefully explain why this was not done.





# **PART A**

## **Cognitive and Motor Development of HIV Infected Children: A Systematic Review**



## **COGNITIVE AND MOTOR DEVELOPMENT IN HIV INFECTED CHILDREN: A SYSTEMATIC REVIEW**

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### **Abstract**

**Introduction:** There is controversial evidence within available research on effects of HIV on cognitive and motor development because of the limitations imposed by study designs, study populations and study methodological quality.

**Aim:** The main objective of the review was to assess evidence on cognitive and motor development in HIV-1 infected children in comparison to uninfected children.

**Methodology:** The following databases were searched: MEDLINE, Google Scholar, AIDSTRIALS, AIDSLINE and CINHAL. These databases were searched from their inception to July 2011 without language restrictions. Analytical observational trials that assessed at least one outcome (cognitive or motor development or 1 of the anthropometric outcomes) between HIV positive and HIV negative children aged 5 years and below or children with a mean age of less than 5 years were selected. Two review authors independently searched for eligible studies, evaluated methodological quality and extracted the data. Meta-analysis was carried out using

Rev Man 5.1 using the risk ratio for categorical data and standard mean difference for continuous data.

**Results:** Fifteen studies with a total of 3 086 participants met the inclusion criteria. HIV infected children were 2.45 times at higher risk of developing cognitive developmental delay than HIV negative children (RR, 95% CI, 1.95, 3.07,  $P < 0.00001$ ). Infected children scored -0.54 less than HIV negative children (SMD 95% CI, -0.70, -0.39, 97,  $p < 0.00001$ ) for cognitive development and -0.68 in motor development (SMD 95% CI, -0.82, -0.55,  $p < 0.00001$ ). The risk of motor developmental delays was 2.95 times in HIV positive compared with HIV negative children (RR 95% CI, 2.19, 3.99,  $p < 0.00001$ ).

**Conclusion:** There appears to be an effect of HIV on motor, cognitive and anthropometric development in infected children. These results highlight the necessity of motor and cognitive interventions for HIV-infected children, focussing on motor and cognitive skills to improve their development and quality of life

## **Introduction**

### **Background**

The World Health Organization estimated that approximately 2.1 million children were living with the Human Immunodeficiency Virus (HIV) infection and in 2009, 370 000 children were newly infected worldwide (WHO, 2009). Approximately 1.8 million children in sub-Saharan Africa are infected with HIV which accounts for 86% of HIV-infected children in the world (WHO, 2009). In 2006, HIV/AIDS claimed the lives of 380 000 children (Joint United Nations Programme on HIV/AIDS, 2006). HIV infects cells of the immune system, destroying or impairing their function. As the infection progresses, the immune system becomes weaker and the person becomes more susceptible to infections. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS). HIV is transmitted through unprotected sexual intercourse (anal or vaginal), transfusion of contaminated blood, sharing of contaminated needles, and vertically transmitted during pregnancy (main mode of infection in young children), childbirth and breastfeeding (WHO, 2009).

### **Description of the condition**

HIV involvement in the central nervous system has been reported since 1983 and HIV associated dementia (HAD) has been identified to be the major cause of cognitive and motor dysfunction observed in 50% of infected children (Price, Brew, Sidtis, Rosenblum, Scheck, & Cleary, 1988, p. 4840). HIV-1 penetrates the brain in the early phase of infection possibly by slipping through the blood brain barrier and targets and infects glial cells, from which it later secretes neurotoxins that lead to neuronal damage and death (Clifford, 2002, p. 540). The magnitude of neuronal damage may be linked to the degree of clinical neurologic deficits (Dubé, Benton, Cruess, Evans, 2005, p. 238).

HIV infection in the developing Central Nervous System (CNS) of children, known as HIV encephalopathy is characterized by either a progressive or static loss of previously acquired developmental milestones in cognitive, behavioural and motor development (Chase, Ware, Hittelman, Blasini, Smith, Llorente, 2000, p. 9). It is common in rapid progressors with a positive test early and in utero infection during the last weeks of pregnancy, which is the period of fastest brain growth (Pearson, McGrath, Nozyce, Nichols, Raskino, Brouwers, 2000, p. 8).

HAART is an effective therapy for the reduction of viral load, risk of resistance, increase in CD4 count and reduction in mortality (Galletto-Lacour, Yerly, Perneger, Baumberger, Herschel, Perrin, 1996, p. 1338). Childhood mortality is expected to decrease with the introduction of HAART and HIV long-term effects will be of utmost importance to health care providers.

Elevated rates of moderate and severe cognitive impairment among children with HIV have been reported but are attributed to the lack or limited administration of HAART among the children examined (Thomaidis, Bertou, Critselis, Spoulou, Kafetzis, Theodoridou, 2010, p. 7). Although HAART improves the functioning of HIV-1 infected children, some cases of CNS disease where children have scored below average cognitive functioning still exists (Martin, Wolters & Toledo-Tamula, 2006, p. 649). Kim and Rutstein (2010, p. 192), suggested that there is a possibility that antiretrovirals could be contributory factors to poor growth in some instances. The pre and post HAART era identifies compromised cognitive and motor functioning among HIV infected children (Lindsey, Malee, Brouwers & Hughes, 2007 p. 687). This suggests that despite improved treatment that even reduced neurologic complications, HIV infection still penetrates the central nervous system. Lindsey et al. (2007, p. 687) argue that neurodevelopment may be affected by genetic, health, disease, treatment, and/or psychosocial factors in the HAART era.

Environmental factors affecting cognitive and motor development where children live include: poverty, violence and abuse, and prenatal drug abuse (Kullgren, Morris, Bachanas, Jones, 2004, p. 250). Chase et al. (2000, p. 9) stated that there is no significant difference in cognitive and

motor performance in drug exposed and none exposed infants. Nutritional deficiencies such as the lack of vitamin A, iodine, iron, inadequate caloric and protein intake affect both physical and cognitive development (Engle, Black, Behrman, de Mello, 2007, p. 230).

The human brain growth velocity is at its peak at term and preterm delivery leads to a permanent reduction in final brain size (Cooke & Hughes, 2003, p. 486). This may lead to an increased risk of cognitive motor and performance deficits (Chase et al., 2003, p. 8).

A number of systematic reviews have been conducted to address developmental outcomes in children infected with HIV/AIDS. However these studies have found it difficult to carry out a meta-analysis on the effects of HIV on neurodevelopment due to diversity of measuring instruments and age of participants (Sherr, 2010, p. 397; Newman, 1995). In Sherr 92009, p. 397) some studies compared HIV positive with seroreverters, whereas others compared both of these two with uninfected/unexposed control groups yet another group compared HIV positive with uninfected/unexposed control groups only. Some groups had sub analysis components according to severity of disease and presence of drug levels in the infant, which further compounded the comparability of studies.

A review by Abubakar (2008, p. 885) on seven studies did not draw firm conclusions on the effects and magnitude of HIV infection on the development of children in Sub Sahara Africa due to limited number of studies. The relationship between neurodevelopment and anthropometry has never been evaluated by previous reviews.

## **Problem statement**

The global epidemic of HIV continues with an estimated 2.2 million children under 15 years of age worldwide living with HIV and 640 000 newly infected in 2004 (WHO, 2009). HIV crosses the blood–brain barrier which may lead to neuronal damage and death.

There is controversial evidence within available research on the effects of HIV on cognitive and motor development because of the limitations imposed by study designs, study populations and study methodological quality. The systematic review adds more evidence on the effects and prevalence of vertical HIV infection on cognitive and motor development in HIV infected children ages 5 years and below by summarizing all available evidence within the proposed stipulated criteria. The degree of risk of bias and confounding can be assessed by critical appraisal of methodological quality and a meta-analysis in a systematic review which the previous reviews have not addressed.

### **Significance of the Study**

As quality of life becomes a more essential concern in the management of HIV, better awareness of cognitive and motor manifestations of HIV is critical. In an effort to guide clinicians and researchers with respect to the prevalence of HIV associated cognitive and motor effects on development, we conducted a quantitative systematic review of the research literature.

### **Aims**

To conduct a systematic review of published research to establish the effects and the prevalence of HIV infection on cognitive and motor development in children.

### **Objectives**

- To assess evidence on cognitive and motor development in HIV-1 infected children
- To describe anthropometric outcomes including: weight for age, weight for height, height for age and head circumference in children with HIV infection.
- To assess the methodological quality of studies on the cognitive and motor development of HIV infected children.



## **Ethical Review**

The final copy of the research protocol was presented to the Ethics committee of Stellenbosch University. Ethical review of the study was not deemed necessary because of the use of data that is available in the public domain.

## **Methodology**

### **Criteria for considering studies for this review**

#### **Types of studies**

Analytical observational trials that assessed at least one outcome (cognitive or motor development or one of the anthropometric outcomes) and comparing HIV positive and HIV negative children. The topic of study does not permit RCT's since there is no intervention in the study therefore studies monitoring a developmental outcome and compare two groups of HIV infected and negative children will be included in this review.

#### **Participants**

HIV positive children compared with HIV negative children aged one month to five years or mean age of participants less than five years from Urban or rural setting.

#### **Types of outcome measures**

##### **Primary outcomes**

Cognitive and motor development in children

## **Secondary outcomes**

Anthropometric outcomes: weight for age, weight for height, height for age and head circumference.

## **Exclusion Criteria**

- Trials on children infected with HIV through blood transfusion to reduce bias on the results by selecting vertically transmitted children who form the majority of the study population
- Trials on HIV with other co morbidities (haemophilia) since it will be difficult to relate deficits to HIV or haemophilia
- Trials without a comparison group.

## **Search methods for identification of studies**

### **Electronic searches**

The following databases were searched: MEDLINE, Google Scholar, AIDSTRIALS, AIDSLINE and CINHALL.

The search included published works from inception to July 2011 without language restrictions. A specific search strategy to identify analytical observational studies was used in conjunction with medical subject headings and text words specific for cognitive and motor development, anthropometry and HIV. When searching different databases, the search strategy was modified. The search for articles was conducted between 10<sup>th</sup> May and 30<sup>th</sup> July 2011.

**Search Terms:** cognitive, motor, development, children, encephalopathy, Human immunodeficiency Virus (HIV), AIDS, neurodevelopment, height, weight, anthropometry, cohort, cross-sectional, experimental children, infants.

### **Search strategy for MEDLINE**

1. Cognitive
2. Motor
3. Cognit\$
4. Physical
5. Anthropomet\$
6. Height
7. Weight
8. Encephalopathy
9. Development\$
10. Neurodevelopment
11. Psychomotor
12. Incapacity
13. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. HIV
15. AIDS
16. Human Immunodeficiency Virus
17. Acquired Immunodeficiency Syndrome
18. 13 AND 14 OR 15 OR 16 OR 17
19. Child
20. Children

21. Infants

22. Toddler\$

23. 18 AND 19 OR 20 OR 21 OR 22

### **Searching of other sources**

Reference lists of all relevant articles and Google books on child development were searched for further relevant studies. Proceedings and abstracts from AIDS conferences and global meetings were researched. Authors in the field of neurology and HIV/AIDS to assist with identifying relevant articles to be assessed for eligibility were contacted.

## **Data Collection and Analysis**

### **Selection of studies**

The selection of studies for inclusion in a review is very imperative stage of the review process as it identifies all studies that need to be included in the review and if incorrectly done, relevant literature may be excluded.

### **Eligibility**

Two reviewers: (GK, OK) independently assessed titles identified in the above search strategy. If a title was considered to be relevant, its abstract was reviewed to determine whether the article might meet predisposed eligibility criteria (see appendix 2 for a sample of eligibility form). The eligibility form comprised of: type of study (Observational study), participants (HIV infected children compared with HIV negative children) and outcomes presented. An article that did not meet eligibility criteria was rejected. If the title or abstract leave room for doubt that the article cannot definitely be rejected, the full text of the article was obtained. Full text articles which did

not meet the inclusion criteria were excluded. If the article was not rejected, information from it may then be formally extracted using the data extraction form. Disagreements about the inclusion of studies were resolved by referring back to the original article and discussion until consensus was established between the two reviewers.

### **Data extraction and management**

Characteristics of included studies were independently extracted by (GK, OK) using a standardised data extraction form for analytical observational studies (Appendix 5). Data retrieved included: study design (cross-sectional, prospective cohort), study population (number of children, age) and setting, scales used for assessments, outcomes, confounding factors controlled (preterm delivery, substance abuse, socio-economic status, home and environment), number lost to follow up, and type of analysis (statistical methods, univariate/multivariate, adjusting for confounders). Disagreements were resolved by discussion.

### **Reliability and validity**

Inter-rater reliability, internal and external validity were utilised to ensure consistency, generalisation and the relationship between HIV infection and neurodevelopment in children aged 5 years and below. Study selection, data extraction methodological quality was conducted by two independent reviewers (GK, OK). Criteria for study inclusion/exclusion was predetermined and implemented. A pilot of two studies on the data extraction form was done and these pilots were included in the results section.

### **Assessment of methodological quality**

Two reviewers (GK and OK) independently assessed the methodological quality of studies was assessed using the Newcastle Scale for Observational Studies (NOS) (Wells, Shea, O'Connell

Robertson, Peterson, Welch, et al.). A criterion was stipulated to GK and OS which items to award a star to a study before data extraction. The NOS and its stipulated criteria were piloted before being applied. A star was awarded if both reviewers gave an item a star and if there were doubts; reviewers discussed the item and a referred back to the article until consensus was reached.

NOS comprises of three categories: selection, comparability and exposure/outcome. It was chosen mainly for this review because it contains separate questions for cohort and case control studies. It was developed based on threats to validity in nonrandomized studies; these specifically include selection of participants (generalizability or applicability), comparability of study groups, methods for outcome assessment (cohort studies) or ascertainment of exposure (case-control studies), adequacy of follow-up and inter-rater reliability.

The selection category has four items; each item is scored by a star. The outcome/ exposure categories have three items, each to be awarded with a star. However, cross sectional studies were assessed for only two items in the exposure section as the same response item was removed due to its irrelevance to design in this review.

A maximum of two stars can be given for the category of comparability. Cross sectional studies were scored out of eight and cohort studies scored out of nine stars. The table below shows the criteria used to award a star for studies in each numbered item.

**Table 1: Newcastle-Ottawa Scale for Observational Studies (Scoring Criteria)**

<b>Selection</b>	<b>Comparability</b>	<b>Outcome/Exposure</b>
<b>Cross sectional studies (4 stars)</b>	<b>(2 stars)</b>	<b>(2 stars)</b>
1. HIV test for all HIV positive children and exclusion criteria given* 2. Representativeness of the sample of HIV infected children in the community not by sample of convenience* 3. Community controls used* 4. Children were defined as healthy with absence of disease *	Matched with age* controlling of any confounder (Socio economic status, preterm delivery, prenatal drug exposure, home and environment).*	1. Blinded developmental assessment was done* 2. The same scale was used to assess the two groups. *

<b>Cohort Studies (4 stars)</b>	<b>(2 stars)</b>	<b>(3 stars)</b>
1. Representativeness of HIV infected children in the community reason for exclusion specified and if the author stated that the sample represented the community * 2. Participants were from the same community * 3. An HIV test or record determined ascertainment of the exposure* 4. An initial developmental assessment to demonstrate absence of developmental anomalies before enrolment*	Matched with age* controlling of any confounder (Socio economic status, preterm delivery, prenatal drug exposure, home and environment).*	1. Independent blind assessment or record linkage * 2. Follow- up period of one year or more* 3. Dropout rate less than 15% in HIV positive and HIV negative groups*

### **Measures of treatment**

Data were analysed using Review Manager 5.1. Dichotomous data were analysed with Mantel-Haenszel methods and risk ratios with a 95% confidence interval. Standardised mean difference (SMD) with 95% confidence intervals for continuous data was used. SMD was selected due to variability in rating scales for the assessment of cognitive and motor development.

### **Assessment of heterogeneity**

A random effects method was used to easily identify heterogeneity with wider confidence intervals. Statistical heterogeneity was assessed by using a chi-squared test on N-1 degrees of freedom. Inconsistency across the studies in the meta-analysis was quantified by means of the  $I^2$  statistic.

Heterogeneity was considered to be statistically significant if the p-value for the Chi squared test was  $< 0.10$ .  $I^2 = 0$  to 30 % was low heterogeneity,  $I^2$  value of  $>30$  to 60 moderate,  $>60$  to 75 substantial and  $>75\%$  was regarded as considerable heterogeneity.

### **Data synthesis**

All included articles were analysed by Review Manager (version 5.1) Cochrane software. Data from studies with similar participants, outcomes, and study designs were pooled in a meta-analysis if there was no significant statistical heterogeneity. A fixed-effect model was employed if there was low heterogeneity ( $I^2 = 0$  to 30) for the main effect outcomes. Where heterogeneity of more than 30% existed, the random-effects model was incorporated.



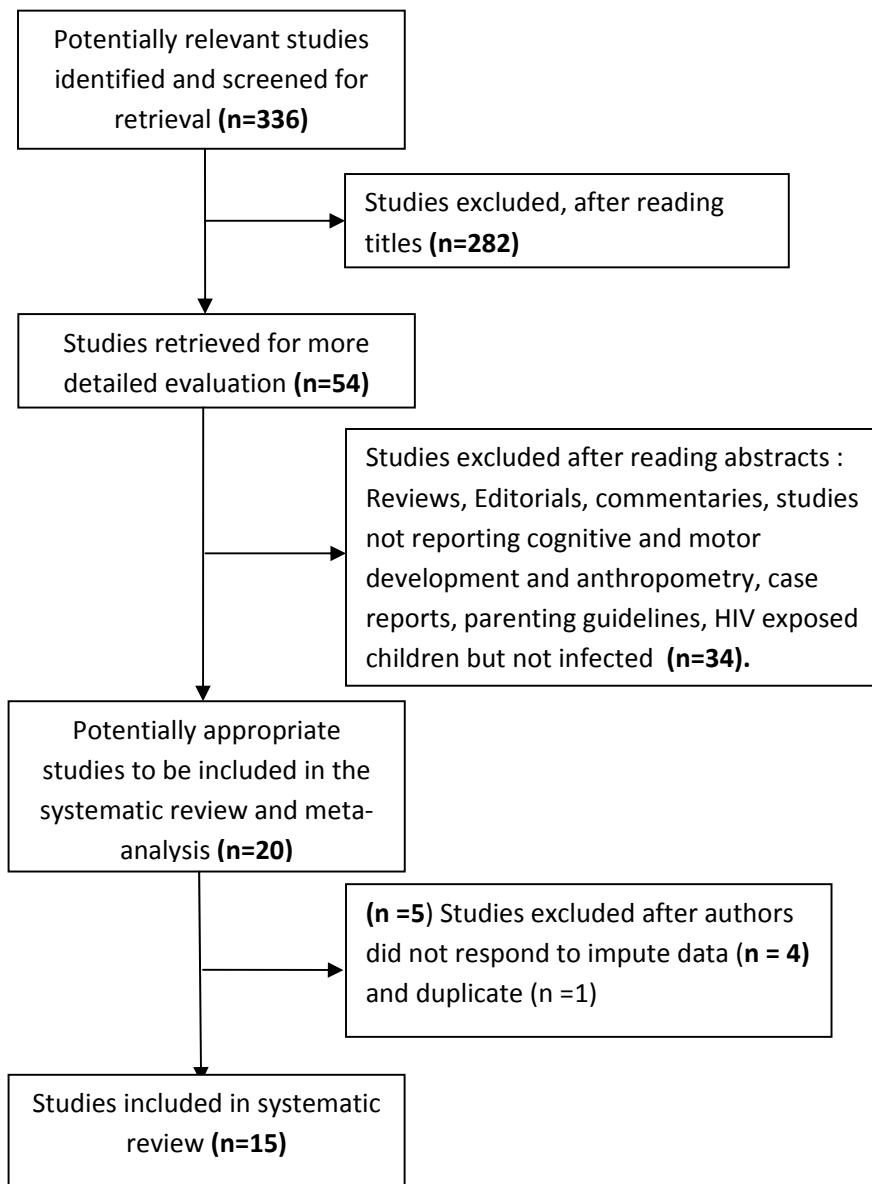
### **Subgroup analysis and investigation of heterogeneity**

A subgroup analysis was planned prior to the main analysis for primary outcomes only by study design and type of instrument used. However, studies were stratified by study design (cohort and cross sectional) and a subgroup analysis of studies that used Bailey Scales was used to explore heterogeneity of >30% and examine direction of findings.

### **Sensitivity analysis**

Sensitivity analysis to assess heterogeneity and to examine the direction of findings on cognitive and motor outcomes was planned in the protocol stage on studies that did not report blinding of the investigators and ARV/ HAART naïve studies. However sensitivity analysis was applied on anthropometric outcome: weight for age at the results stage to investigate heterogeneity.

## Results



**Figure 1: Flowchart of the screening process**

## Search Results

Figure 1 shows search results. The search strategy initially retrieved 336 titles of which 282 publications were excluded based on the relevance of the title. Following the exclusion of irrelevant titles, 54 abstracts were screened for eligibility. Thirty four publications were excluded after reading abstracts. Only 20 potentially appropriate studies to be included in the systematic review remained. We further excluded 5 studies (4 with missing data and 1 duplicate). Meta-analysis was performed on 15 studies.

## Description of included studies

A total of 15 studies with a total of 3 086 (598 HIV positive and 2 488 HIV negative) participants met the inclusion criteria. Six studies were conducted in Africa, 6 USA, 1 Brazil, 1 Europe and 1 in Haiti. Three studies were cross sectional designs, 9 prospective and 3 retrospective cohorts. Five studies compared HIV positive with seroreverters, whereas 10 compared HIV positive children with both uninfected and seroreverters control groups. Assessments were conducted in hospital settings by 14 studies, at home and (n=1).

**HIV positive group:** All children in the HIV positive group were tested for HIV or the data available showed that they were known HIV cases.

**HIV negative group:** Studies compared HIV positive (seropositive) children with either seroreverters (Exposed to HIV during pregnancy) or HIV negative (seronegative) or both. In studies with more than two comparison groups, two comparison groups were chosen for this review.

**Loss to Follow-up (LTFU):** Loss to follow-up due to death ranged from 0% to 58% in the HIV positive group. LTFU due to any other reasons ranged from 0% to 27 in HIV negative and 29% in HIV positive groups. Antiretroviral treatment was not readily available when studies were in progress in 13 studies. However, loss to follow up did not affect the results of this review because first assessment was chosen in studies with more than 1 assessment when most participants were present.

**Diagnostic criteria:** HIV-1 infection was diagnosed by confirmed antibody tests and the World Health Organisation staging of AIDS.

### **Scales used**

Studies used seven varying neurological scales to evaluate developmental milestones in children: Bailey Scales of Infant Development (n= 8 studies), Kaufman Assessment Battery for Children (n=1), Denver Developmental Screening Test with Clinical Adaptive Test, (n=1), Snijders Oomen Nonverbal Intelligence Test–Revised (n=1), Wechsler Preschool and Primary Scales of Intelligence-Revised, (n =1) and the Kififi scale (n=1).

**Table 2: Characteristics of Included Studies**

First author, Year, Country	Study Design	Participants + Setting	Method used to test HIV	Age scales used
<b>1. Abubakar, 2009 Kenya</b>	Cross sectional Study	31 HIV infected , 17 HIV-seroreverters and 319 seronegative Examined @ home	positive HIV antibody test when > 18 months or a polymerase chain reaction test if < than 18 months	Aged 6 to 35 months. Kififi scale
<b>2. Aylward, 1992. USA</b>	Prospective cohort	96 infants: 45, seronegative, 12 seropositive and 39 Seroreverters hospital setting	HIV antibody test	5.5 to 24 months. BSID II
<b>3. Boivin, 1995 Zaire</b>	Prospective Longitudinal cohort	11 HIV infected, 15 Seroreverters 15 control (hospital near Kimpese)	HIV check blot Test	HIV +: mean age: 54.8 SD: 8.6 Control: 46.2.SD: 12.6 K-ABC
<b>4. Chase, 2000 USA</b>	Multicentre Prospective cohort	421 infants: 77 HIV positive and 344 Seroreverters 6 clinical centres	Presence of 2 or more cultures of peripheral blood mononuclear cells positive for HIV-1	From 7days till 30 months. BSIDII
<b>5. Dobrova-Krol, 2010 Ukraine</b>	Cross Sectional Study	Total: 64: 13 HIV+ institution-reared, 16 negative institution-reared, 16 HIV+ family-reared and 19 HIV negative family-reared children.	Positive viral culture of polymerase chain reaction assay	Mean :50.9 months SON-R &theory of mind
<b>6. Drotar, 1997 Uganda</b>	prospective cohort study	61 HIV positive infants, 234 Seroreverters, and 115 HIV negative	HTV-1 enzyme immunoassay confirmed with Western Blot (WB) HTV-1 DNA polymerase	Enrolled at birth for 24 months. BSID II

		Old Mulago Hospital	chain reaction (PCR) and (ICD) tests	
<b>7.Fishkin, 2000 USA</b>	Retrospective Cohort	40 HIV infected and 40 HIV negative children  Hospital files and clinical programme	Medical records	Ages 3 to 5years. WPPSI-R)
<b>8.Gay, 1995 Haiti</b>	Prospective Cohort	126 Children : 28 HIV infected and 98 Seroreverted children from 18 months	Clinical, immunologic, serologic, and virologic end points	From birth till 24 months. BSID
<b>9. Knight, 2000 USA</b>	Retrospective cohort	20 HIV infected and 25 Seroreverters aged 3 to 30 months old family based care in a hospital	Positive HIV antibodies after 18months	3 till 30 months old.  BSID
<b>10.Lindsey, 2007 USA</b>	Longitudinal prospective cohort study	838 Seroreverters and 91 HIV positive  Hospital setting	Positive HIV antibody >18months	1month to 3years.  BSID
<b>11.McGrath, 2006 Tanzania</b>	Prospective Cohort	276: 55HIV positive and 221 seroreverters Muhimbi hospital	Polymerase chain reaction (PCR) @>18months	Birth till 24 months. BSID-II
<b>12. Miller, 1993 USA</b>	Retrospective cohort	37 Seroreverted and 51 HIV Positive children. Children's Hospital setting	ELISA and Western Blot analysis after 15 mo of age, or WHO clinical signs	Mean: 21HIV + Mean: 19control. Weight scale
<b>13. Msellati, 2003 Rwanda</b>	prospective cohort study	218 Seroreverters and HIV+ compared with 218 seropositive infants.	WHO clinical case definition of AIDS in children and HIV-1 antibody serostatus > 15	From birth till 24 months. Modified Denver score

		Hospital Setting	months of age	
<b>14. Tahan 2006 Brazil</b>	progressive prospective and cross sectional	88 HIV positive children and 84 Seroreverters  Clinical Hospital of UFPR.	Serological and/or virologic tests	1month till 36 months. CAT/CLAMS, DDST
<b>15. Van Rie , 2007 Republic of Congo</b>	Cross sectional study	35 HIV-infected, 35 Seroreverters and 90 seronegative  Hospital setting	Enzyme-linked Immunosorbent assay– based	Median: HIV + 45.7, Reverters: 45.6. BSID

### Quality Assessment of included studies

Studies with nine items and eight on the cross sectional in the Newcastle-Ottawa Scale were considered satisfactory and statistical analysis (multivariate or risk adjusted) deemed studies as of high methodological quality. Only four studies did a multivariate analysis or other acceptable methods of adjusting to ensure that studies did not report biased results to minimize the potential for confounding. Among cohort studies 1 study scored 9 stars, 6 scored 8 stars and 5 scored 7 stars. Among cross sectional studies 1 study scored a total score of 8 and the other 2 scored 7. Intent to treat was done in 11 studies and 10 studies blinded examiners. In overall, studies were of moderate quality.

**Table 3: Quality of Included Studies (Newcastle for Observational Studies)**

Cross Sectional				
First Author	Selection	Comparability	Exposure	Total
Abubakar	☼☼☼☼	☼☼	☼☼	8
Dobrova-Krol	☼☼☼☼	☼☼	☼	7
Van Rie	☼☼☼☼	☼☼	☼	7

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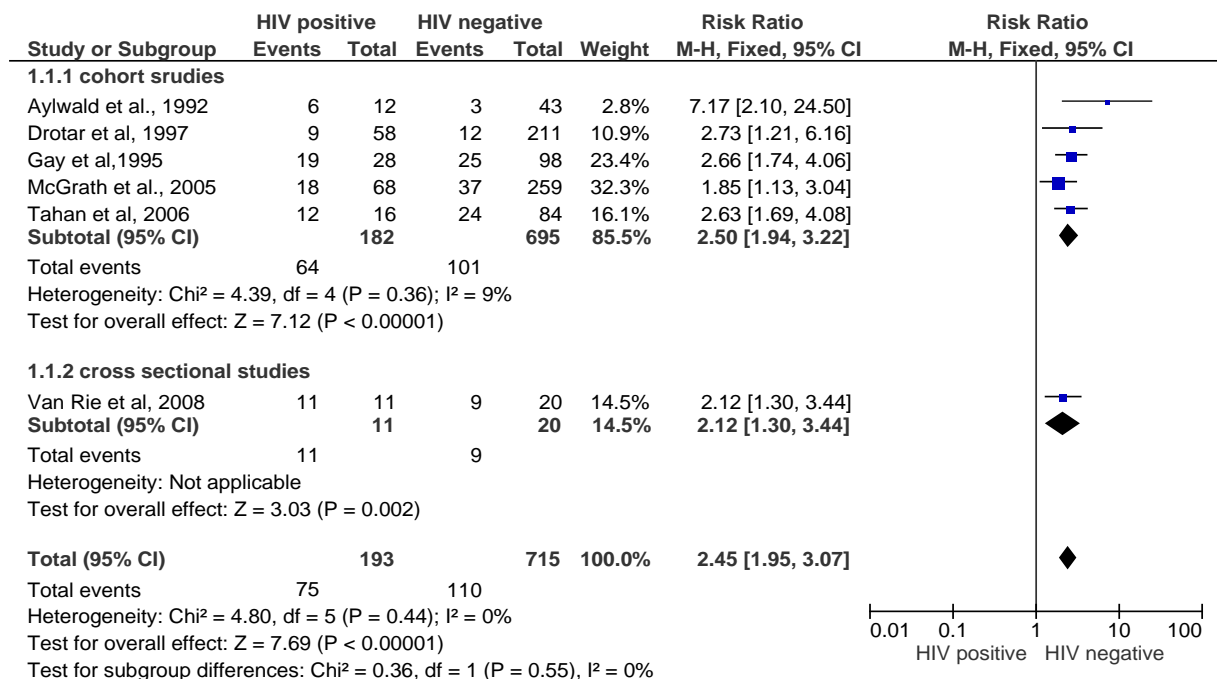
<b>Cohort studies</b>				
<b>First Author</b>	<b>Selection</b>	<b>Comparability</b>	<b>Outcome</b>	<b>Total stars</b>
Aylwald	***	**	** 6% LTFU	7
Boivin	***	**	***	8
Chase	****	** Covariate in the modelling process. <b>High Quality</b>	**3.8% LTFU and 13HIV+ died	8
Fishkin	***	**	**	7
Drotar	****	** Stratified group means for home and environment. <b>High Quality</b>	**7% LTFU	8
Gay	****	**	**3%LTFU, 56% died in HIV+ group and 1 in HIV	8
Knight	****	**	***	9
Lindsey	****	** Univariate analysis <b>High Quality</b>	**13%HIV: 6% HIV+ LTFU	8
Mc Grath	***	**	**11%LTFU. 27% :HIV+ 29%HIV- died	7
Miller	****	**	**	8
Msellati	***	** Analysis of variance for prematurity <b>High Quality</b>	**5.5%LTFU. 58% cumulative mortality	7
Tahan	****	*	** 24% loss of LTFU	7

## Cognitive development

A total of 12 studies; 1 with 2 subgroups (family and institutionally reared children) with a total of 2 206 participants (429 HIV positive and 1 777 HIV negative) reported sufficient data on cognitive development.

### Children with cognitive developmental delay

Six studies reported on cases of cognitive development in HIV positive and negative children (Aylwald 1992; Drotar 1997; Gay 1995; McGrath 2006; Tahan 2006; Van Rie 2008). Five of the studies used the BSID and 1 used the Clinical Adaptive Test. A total of 908 children: 193 HIV positive and 715 HIV negative children were analysed (Figure 2). HIV positive children were 2.45 times at higher risk of developing developmental delay than HIV negative children (95% CI, 1.95, 3.07,  $p < 0.00001$ ). Heterogeneity was not important:  $\text{Chi}^2 = 4.80$ ,  $\text{df} = 5$  ( $p = 0.44$ );  $I^2 = 0\%$ .

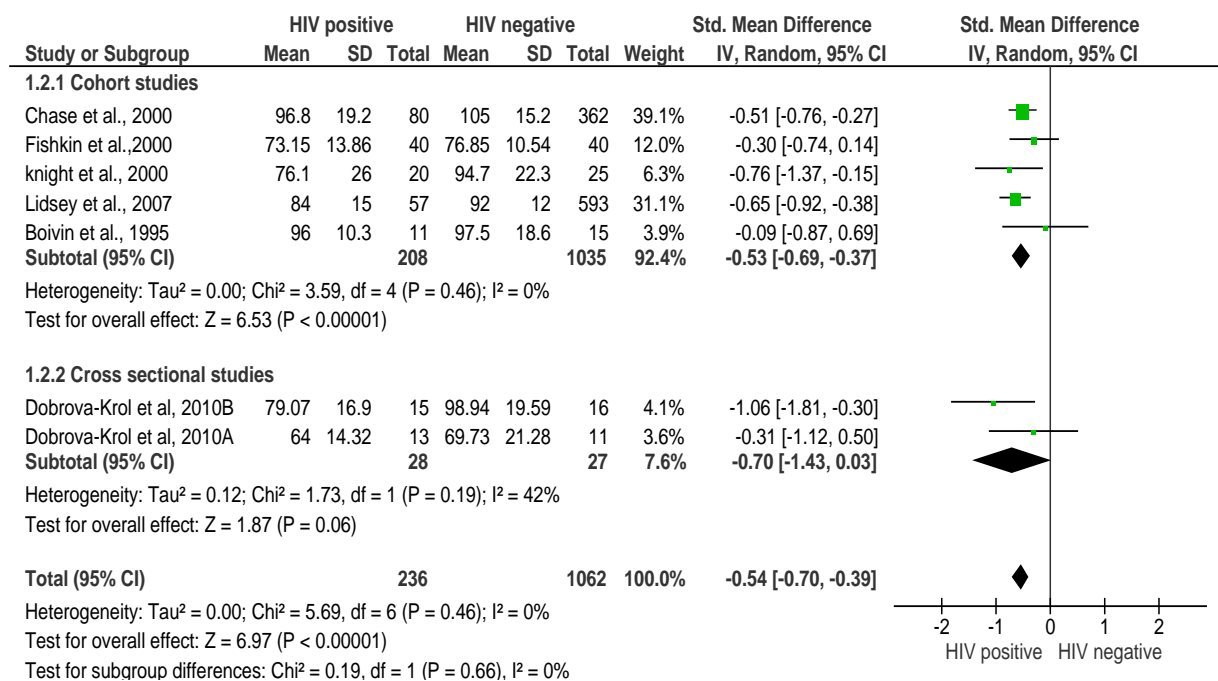


**Figure 2: HIV positive and negative children with cognitive development delay**

### Cognitive quotient of HIV positive and negative children

Six studies, 1 with 2 subgroups (family and institutionalised children) reported on cases of cognitive development in HIV positive and negative children (Boivin 1996; Chase 2000; Fishkin 2000; Knight 2000; Tahan 2006; Dobrova- Krol 2010A; Dobrova- Krol 2010B; Lindsey 2007). Three of the studies used the BSID, K-ABC (n=1), WPPSI: (n=1), SON-R (n=1). A total of 1 298 children (236 HIV positive and 1 062 HIV negative) were analysed.

HIV infected children scored a significantly lower cognitive mean quotient than their HIV negative counterparts with a standard mean difference of -0.54 (SMD 95% CI, -0.70, -0.39,  $p < 0.00001$ ) heterogeneity between studies was not important:  $\text{Chi}^2 = 5.69$ ,  $\text{df} = 6$  ( $p = 0.46$ );  $I^2 = 0\%$ .



**Figure 3: Cognitive developmental mean quotient of HIV positive and negative children**

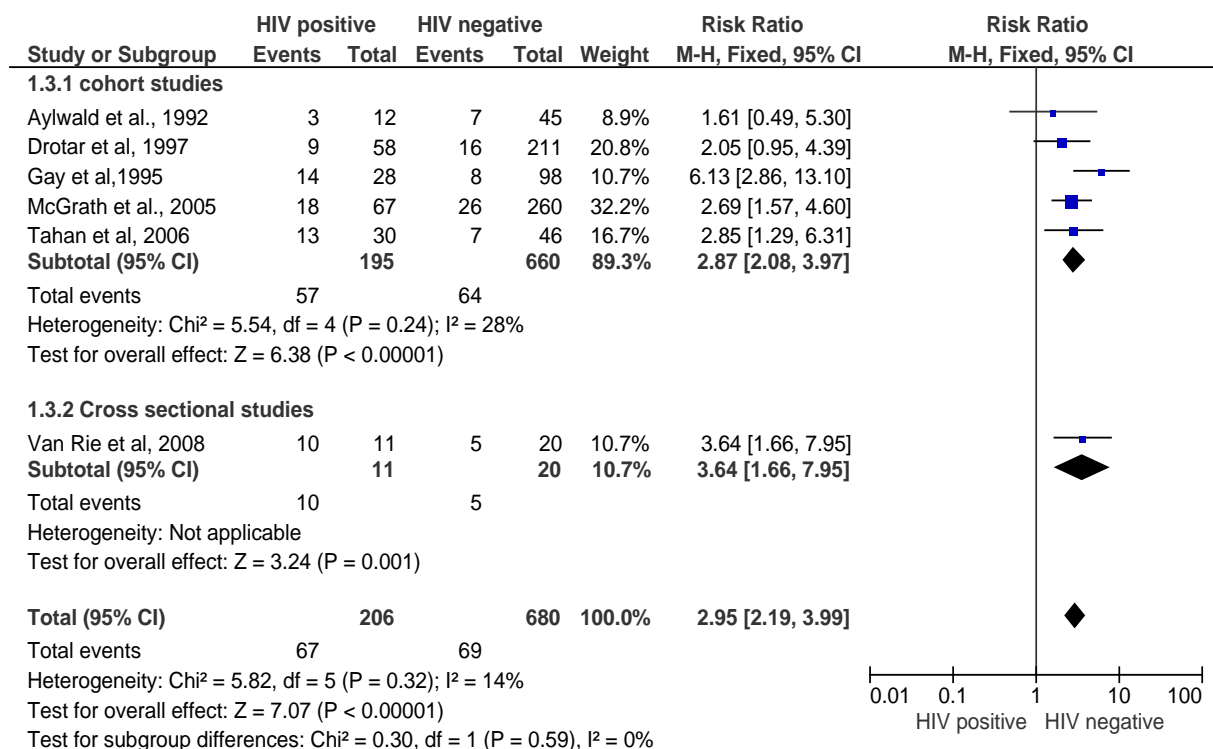
## Motor Development

A total of 11 studies, 1 with 2 subgroups (gross motor and fine motor) and 2 822 participants (476 HIV positive and 2 346 HIV negative) reported sufficient data on motor development.

### Children with motor developmental delay

Five studies (Aylwald 1992; Drotar 1997; Gay 1995; Mc Grath 2005; Van Rie 2008) reported on motor development in HIV positive and negative children. Five of 6 studies used Bailey Scales of infant development. A total of 886 children: 206 HIV positive and 680 HIV negative were analysed.

HIV positive children were 2.95 times a risk of developing motor developmental delays than HIV negative children (RR, 95% CI, 2.95 2.19, 3.99,  $p = < 0.00001$ ). There was a low defined heterogeneity between studies;  $\text{Tau}^2 = 0.02$ ;  $\text{Chi}^2 = 5.82$ ,  $\text{df} = 5$  ( $p = 0.32$ );  $I^2 = 14\%$ .

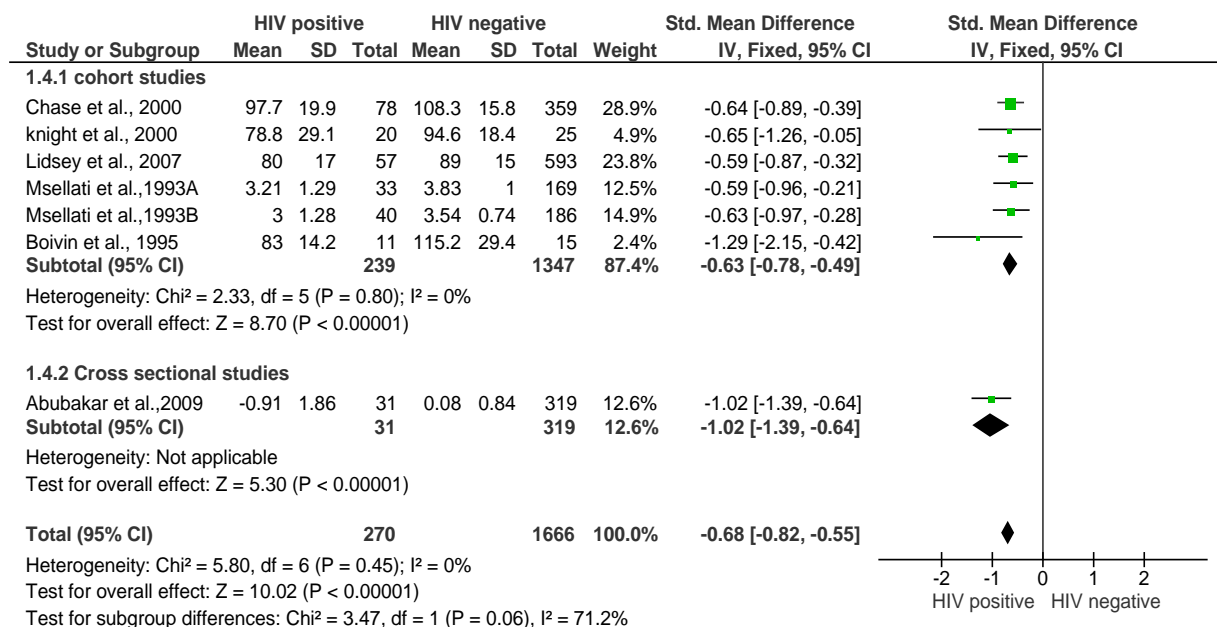


**Figure 4: Motor developmental delay in HIV positive and negative children**

Six studies, 1 with 2 subgroups (gross motor and fine motor) (Abubakar 2009; Chase 2000; Knight 2000; Lindsey 2007; Msellati 1993A; Msellati 1993B and Boivin 1995) had a total of 1 936 children (270 HIV positive and 1 666 HIV negative). BSID was used by three studies, modified Denver scale (n=1), K-ABC (n=1), Kififi scale (n=1).

HIV infected children scored a significantly lower mean quotient than that of HIV negative children with a Standard Mean Difference of -0.68 (SMD 95% CI, -0.82, -0.55,  $p < 0.00001$ ). Heterogeneity was not important:  $\text{Chi}^2 = 5.80$ ,  $\text{df} = 6$  ( $p = 0.45$ );  $I^2 = 0\%$ .

However, there was substantial heterogeneity between subgroups of cohort and cross sectional studies: Test for subgroup differences:  $\text{Chi}^2 = 3.47$ ,  $\text{df} = 1$  ( $p = 0.06$ ),  $I^2 = 71.2\%$ .

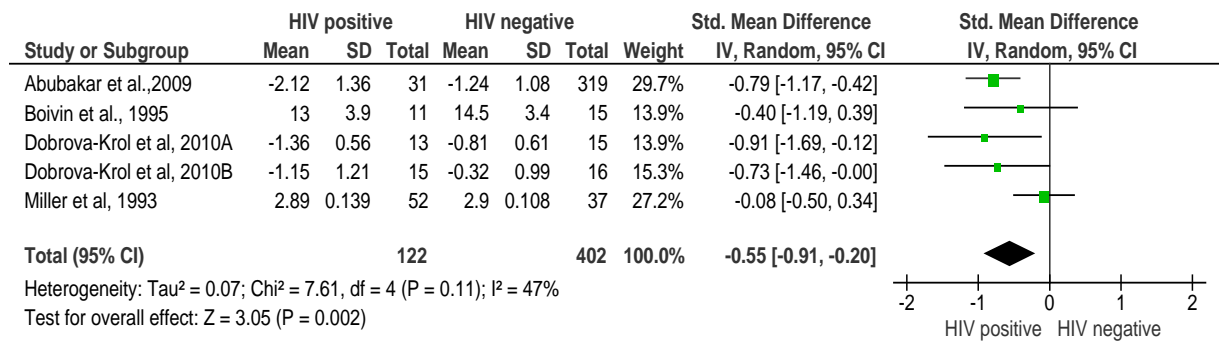


**Figure 5 : Motor Developmental mean quotient in HIV positive and negative children**

## Anthropometric Outcomes

### Weight for age

Four studies (Abubakar 2009; Boivin 1995; Dobrova-Krol 2010A; Dobrova-Krol 2010B; Miller 1993), 1 with 2 subgroups (family and institutionalised children) with a total of 524 participants reported on weight for age. HIV positive children scored a significant lower mean weight for age quotient with a SMD of -0.55 compared to HIV negative children of the same age (SMD, 95% CI, 0.91, -0.20,  $p = 0.002$ ). Heterogeneity was moderate:  $\text{Chi}^2 = 7.61$ ,  $\text{df} = 4$  ( $p = 0.11$ );  $I^2 = 47\%$ .



**Figure 6: Weight for age among HIV positive and negative children**

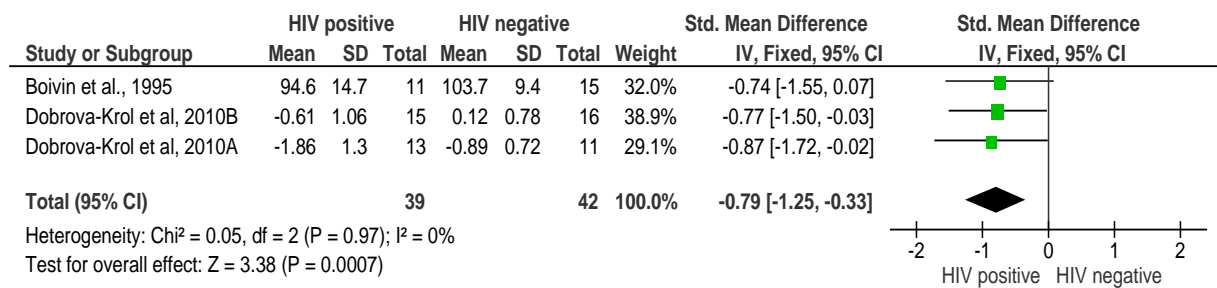
### Weight for height

Boivin (1995) was the only study to report weight for height with 26 participants: 11 HIV positive and 15 HIV negative. There was no significant difference in weight for age for HIV infected children (SMD -0.43, 95% CI -1.22, 0.36  $p = 0.28$ ).

## Height for age

Two studies, 1 with 2 subgroups (family and institutionalised children) reported height for age (Boivin 1995; Dobrova-Krol 2010 A; Dobrova-Krol B) with a total of 90 participants: 40 HIV positive and 50 HIV negative.

HIV infected children had an SMD of -0.79 lower height for age than HIV negative (95% CI -1.25, -0.33,  $p = < 0.0007$ ). Studies were homogenous:  $\tau^2 = 0.00$ ;  $\chi^2 = 0.05$ ,  $df = 2$  ( $p = 0.97$ );  $I^2 = 0\%$ .



**Figure 7: Height for Age among HIV positive and negative children**

## Head Circumference

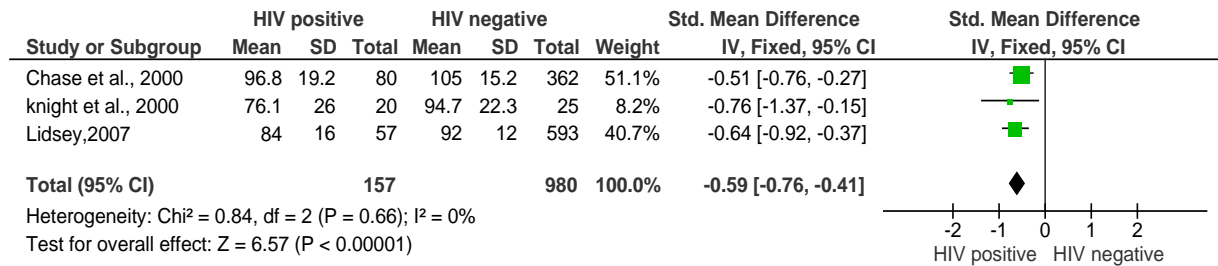
Boivin (1995) was the only study to report head circumference with 26 participants: 11 HIV positive and 15 HIV negative. There was no significant difference in the head circumference of HIV infected children (SMD -0.67, 95% CI -1.47, 0.13,  $p = 0.10$ ).

## Subgroup Analyses

### Cognitive Developmental mean quotient for studies that measured development using the Bailey Scales

Three studies that used Bailey Scales (Chase 2000; Knight 2000; and Lindsey 2007) were analysed in a sub group to assess direction of findings. Studies were homogenous:  $\chi^2 = 0.84$ ,  $df$

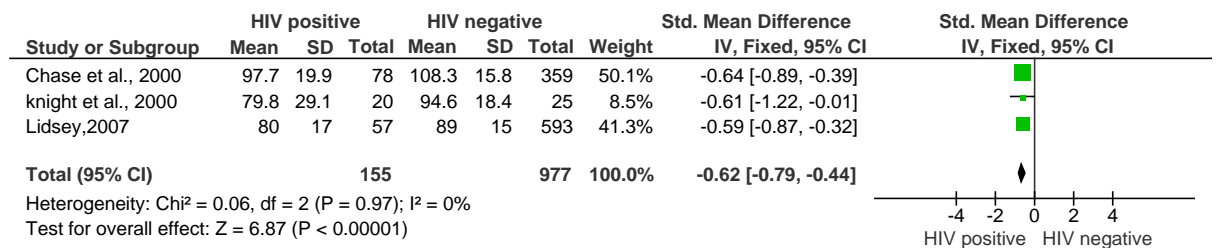
= 2 ( $p = 0.66$ );  $I^2 = 0\%$ . HIV infected children scored -0.59 significantly lower than HIV positive children (SMD 95% CI -0.76, -0.41,  $p < 0.00001$ ).



**Figure 8: Cognitive developmental mean quotient for studies that measured development using the Bailey Scales**

**Motor developmental mean quotient for studies that measured development using the Bailey Scales**

A subgroup analysis of studies that used Bailey Scales (Chase 2000; Knight 2000; and Lindsey 2007) was used to explore heterogeneity. Heterogeneity between studies was not important:  $\text{Chi}^2 = 0.06$ ,  $\text{df} = 2$  ( $P = 0.97$ );  $I^2 = 0\%$ ). HIV infected children scored a significantly lower motor mean quotient in studies that used Bailey Scales -0.62 SMD 95% CI, -0.79, -0.44,  $p < 0.00001$ ).



**Figure 9: Motor developmental mean quotient for studies that measured development using the Bailey Scales**



## **Sensitivity Analysis results**

### **Cognitive development (Standard Mean Difference)**

Efficacy of ARV in reducing developmental delay was assessed by comparing studies which used ARV (Lindsey; Dobrova- Krol A; Dobrova-Krol B) therapy and those which did not (n=4) in a sensitivity analysis. Antiretroviral treatment studies did not show to be effective in reducing cognitive deficits (SMD -0.66 95%CI, -0.91, -0.40,  $p < 0.00001$ , heterogeneity:  $\text{Chi}^2 = 1.77$ ,  $\text{df} = 2$  ( $P = 0.41$ );  $I^2 = 0\%$ ) compared HAART naive studies (SMD-0.47 95% CI,-0.66, -0.27,  $p < 0.00001$ , heterogeneity:  $\text{Chi}^2 = 2.48$ ,  $\text{df} = 3$  ( $p = 0.48$ );  $I^2 = 0\%$ ).

### **Motor Development (Standard Mean Difference)**

Sensitivity Analysis on studies that blinded the examiner (n=5) and those which did not blind the examiner (n=2) were done. Both results were significant but studies that blinded the examiner had higher difference (-0.76 SMD 95%CI, -0.95, -0.56,  $p < 0.00001$ ), heterogeneity  $\text{Chi}^2 = 4.70$ ,  $\text{df} = 4$  ( $P = 0.32$ );  $I^2 = 15\%$ ) than studies that did not report blinding (-0.62, 95% CI, -0.80, -0.43,  $p < 0.00001$ ). Heterogeneity was not important:  $\text{Chi}^2 = 0.06$ ,  $\text{df} = 1$  ( $p = 0.81$ );  $I^2 = 0\%$ .

### **Weight for age**

Miller (1993) was the only trial with a birth weight and a sensitivity analysis of studies that used any other weight was used to explore heterogeneity. Studies showed homogenous results (-0.75 SMD, 95%CI, -1.03, -0.46,  $P < 0.00001$ ), heterogeneity of :  $\text{Chi}^2 = 0.96$ ,  $\text{df} = 3$  ( $p = 0.81$ );  $I^2 = 0\%$ .

## Discussion

### Summary of main results

This comprehensive assessment of available literature identified 15 studies that provided objective assessments of cognitive/ and motor outcomes/ and anthropometric outcomes in HIV infected children compared with HIV negative children. This included a total of 3 086 participants: (598 HIV positive and 2 486 HIV negative). Studies included 9 prospective and 3 retrospective cohort studies and 3 cross sectional. A total of 13 studies assessed ART naive participants and 2 studies assessed children on HAART. Participants had a mean age or were 5 years of age and less using various scales of developmental assessment. HIV infected children were 2.45 times at higher risk of developing cognitive developmental delay than HIV negative children (RR, 95% CI, 1.95, 3.07,  $p < 0.00001$ ).

Infected children scored -0.54 less than HIV negative children (SMD 95% CI, 0.70, -0.39,  $p < 0.00001$ ) for cognitive development and -0.68 in motor development (SMD 95% CI, 2.19, 3.99,  $p < 0.00001$ ). The risk of motor developmental delays was 2.95 times more likely in HIV positive children compared to HIV negative children (RR 95% CI, 2.15, 4.18,  $p < 0.00001$ ).

However, more evidence is needed on evaluating children on HAART to substantiate its effect on cognitive and motor deficits in HIV infected children aged less than 5 years.

### Overall completeness and applicability of evidence

We identified 336 studies and 15 met the inclusion criteria with a total of 3 086 participants. A meta-analysis in this review examined cognitive and motor outcomes using standardised assessments.

The results of this review substantiate the evidence that HIV infection affects cognitive and motor development in children negatively. Deficits were mostly manifested in motor development in terms of severity.

Weight for age and height for age reported sufficient data to be pooled in to a meta-analysis. A significant growth reduction in height for age and weight for age in HIV infected children was

evident. However, physical growth delays of HIV-infected children were not significant in comparison to HIV-negative children in head circumference and weight for height.

Heterogeneity between studies ranged from 0 to 42% in cognitive and motor outcomes and 0% to 47% in anthropometric outcomes. Subgroup analysis with Bailey Scales showed homogenous results.

The design of the study influenced investigations of neurological impact of HIV in children; the delay in cross sectional studies was higher than that of cohort studies for 3 out of 4 outcome measures. This may suggest that cross sectional studies may overestimate the developmental delay or confounding factors may be at a peak at the point of measurement.

Most assessment tools for cognitive and motor development were developed and validated in USA and Europe and only 3 studies from Africa (Abubakar 2010; Boivin 1995; Msellati 1993) in this review developed their own assessment tool. African children scored lower (Van Rie, 2007) than USA children on studies that used internationally validated tools and this suggests modification of assessment tools to assess African children within their cultural context.

The long term effect of HIV infection on neurological involvement is difficult to ascertain because of high attrition rates ranging from 0% (Abubakar 2007) to 58% cumulative mortality (Msellati 1993). HIV infected children died before their second birthday.

Only two studies (Lindsey 2007; Dobrova-Krol 2010) in this review assessed participants on HAART. These 2 studies showed that children on HAART scored lower than HAART naive children in a sensitivity analysis. The significance of these results is difficult to ascertain due to limited studies and confounding factors identified (Dobrova-Krol 2010, assessed 1 group of institutionalised children). Developmental delays in HIV infected children can also be caused by an adverse rearing environment (Kullgren et al., 2004, p. 251). HAART treatment has been proven to prolong the lives of HIV infected children (Scalco, 2004, p. 25). More evidence is needed to determine its effect in reducing developmental delays and for longitudinal studies with minimal loss to follow up.

Studies which controlled at least 1 confounding factor (socioeconomic status, preterm delivery, maternal drug use and home and environment) were appraised in the comparability section,

however studies did not control all four confounding factors which may also affect the development of children and may result in an overestimation of the developmental deficits.

### **Limitations**

- Five studies compared HIV positive children with seroreverters making it difficult to control the effects of maternal illness.
- Studies that used a mean age of less than 5 years (Boivin 1995; Dobrova-Krol 2010) were included and some of the children in those studies may be older than 5 years.
- Efforts at contacting four authors to impute quantified results for the outcomes (two presented in graphs, one analysed with and a t test and one in z scores for anthropometric outcomes) proved unsuccessful as some of the email contacts were no longer active for two authors and two did not respond. One author was contacted for translation of an Italian study to English and the study could not be translated (Piazza, 1995).
- The systematic review was based on relatively a few articles and methodological weakness could influence conclusions of this study.
- Considerable variability across the studies in terms of methods used and reporting of findings could possibly limit comparison of results.

### **Quality of the evidence**

Four studies were regarded as of high quality. A total of nine studies blinded the examiners and twelve studies performed a baseline examination. Loss to follow up was accommodated by choosing the first assessment when all participants were present. Controlling for confounding was done by fourteen studies with one or more factors which may affect neurodevelopment. A total of ten studies used an intention to treat analysis.

### **Agreements and disagreements with other studies or reviews**

This systematic review provides evidence that HIV delays cognitive, motor development weight for age and height for age in children aged 5 and less than 5 years. A met analysis was done in

conjunction with critical methodological quality appraisal to provide more precise, less biased and reliable evidence.

The results of this review correspond to those by Abubakar et al. (2008, p.880), who established that motor development is the most apparent in terms of severity, early onset and persistence across age groups. White et al. (1995:) reported that the median rate of neuropsychological impairment based on test performance was 35% in HIV positive and 12% in HIV negative patients in a review of 57 studies. However, Newman et al. (1995, p.1211) found that there was no significant variation in the neuropsychological testing results amongst symptomatic and asymptomatic participants, as well as baseline impairment in seropositive participants.

### **Author's conclusions**

HIV infected children are slower in aspects of cognitive and motor development compared to their HIV negative counterparts. They also showed delays in anthropometric outcomes; weight for age and height for age. Study design influenced results of the studies with children scoring more on cross sectional than cohort studies. There is still need to develop culturally appropriate or standardise neurodevelopment tools as most African studies still rely on international tools. More evidence is needed on the effectiveness of HAART in reducing cognitive and motor delay. Controlling for confounding in observational studies is a big problem which needs urgent attention and confounding may lead to over estimation of effects. Sub group analysis with bailey scales of infant development resulted in homogenous results; this may suggest further reviews on variety of neurodevelopment assessment tools. These results highlight the necessity of cognitive and motor interventions for HIV infected children focusing on cognitive and motor skills to improve their development and quality of life.

### **Implications for nursing practice**

The HIV epidemic is growing and may result in neurodevelopmental delays in infected children. Neurodevelopmental assessments should be a compulsory assessment to all HIV infected

children as routine screening protocols. This will ensure monitoring disease progression and effects on the nervous system for immediate, appropriate, referral for further treatment. Staff training and continuous education programmes on screening and conducting developmental tests may improve identification of delays on time. Screening tools should be improved and their effectiveness increased by simplifying the current tools to fit into different cultural contexts. Developmental tools developed in Africa should be tried in developed countries to assess their reliability and validity.

### **Implications for nursing education and research**

The incidence of HIV is highest in Africa; therefore more research needs to be conducted on its effects on neurodevelopment. The effectiveness of HAART in reducing neurodevelopmental deficits needs more research in Africa. Other interventions such as massage therapy need to be evaluated in the African context for their effectiveness in increasing cognitive, motor development and cd4 count.

Anthropometry should be performed in all studies conducted on children. More research in Africa may then facilitate the comparison of the results with those of other parts of the world. It is imperative to develop or standardise the current application of neurological examinations to fit into the African context.

### **Dissemination of results**

To conclude the research process a report was compiled and submitted as a thesis at Stellenbosch University. The results of the review will be presented at local and conferences in the department of health and education. Copies will be distributed in the University library and the review will be published in peer reviewed accredited journals.

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# **PART B**

## **APPENDICES**

**Appendix 1****Results of Included Studies**

<b>First author, Year, Country</b>	<b>Confounding factors controlled Lost to follow up</b>	<b>Developmental Outcomes</b>
<b>1. Abubakar, 2009 Kenya</b>	age, gender, socio economic status maternal education, home and environment	Weight for age psychomotor
<b>2. Aylward, 1992 USA</b>	History of IV drug usage, home and environment, maternal age and education. 6% lost to follow up	Cognitive, Motor, Language
<b>3. Boivin, 1995 Zaire</b>	Age, gender, educational level of the mother, and general economic status of the home environment.	Cognition/ Language, Motor, anthropometric outcomes
<b>4. Chase, 2000 USA</b>	Hard drugs exposure, prematurity, socio economic status, maternal education 13 died in HIV positive group. Unexplained loss to follow up	Cognitive and Motor development
<b>5. Dobrova-Krol, 2010 Ukraine</b>	age, socioeconomic status , maternal age, home and environment	Cognitive performance, theory of mind, anthropometric outcomes
<b>6. Drotar, 1997 Uganda</b>	Full-term babies, no birth complications, genetic impairments, or gross neurologic impairments , home and environment. .No infants received zidovudine (AZT). 56% died in HIV + and 1 in control group* 7% lost to follow up	Cognitive and motor development Information processing ability
<b>7. Fishkin, 2000 USA</b>	Socio economic status, ethnicity, prenatal drug exposure 3.75% died after data collection	Gross motor and cognitive development
<b>8. Gay, 1995 Haiti</b>	Ethnicity, maternal prenatal drug use, maternal Separation and death, and birth history. 4 premature babies excluded	Cognitive and Motor development
<b>9. Knight, 2000 USA</b>	prenatally drug exposed. 2 neurological and 2 developmental evaluations. For inclusion	Cognitive and motor development

<b>10. Lindsey, 2007 USA</b>	Maternal ART exposure & history of IV drug use, birth weight, educational level of the primary care giver. Univariate analysis of covariates. HIV +: 13% and 6% HIV negative: 15 % lost to follow up.	Cognitive and Motor development
<b>11. McGrath, 2006 Tanzania</b>	Matched by socio economic status, age and gender, prematurity, marital status. LTFU: 29% HIV- and 27% HIV+ .11 % died	Cognitive and Motor development
<b>12. Miller, 1993 USA</b>	Age, socioeconomic backgrounds. No antiretroviral No loss of follow up	anthropometry : weight
<b>13. Msellati, 2003 Rwanda</b>	Neurologic developmental assessments. Comparable socioeconomic status. 13.9% died	Motor development
<b>14. Tahan 2006 Brazil</b>	Age, one neurological evaluation	Cognitive and Motor development
<b>15. Van Rie , 2007. Republic of Congo</b>	Matched with age and gender, Socioeconomic status. Health status of the parents was assessed @ enrolment.	Mental, cognitive, language and motor development



## Appendix 2

### Eligibility Form

<b>Eligibility form</b>	
Author: eg, Boivin: Year Published, 1995	
<b>Types of study</b>	<b>Tick</b>
Observational trials	✓
<b>Types of participants</b>	
HIV positive children less than 5 years	✓
<b>Outcomes</b>	
Cognitive development	✓
Motor development	✓
Weight for age,	✓
Weight for height,	✓
Height for age	✓
Head circumference.	✓

### Appendix 3

#### Characteristics of Excluded Studies

First author (in alphabetical order)	Study design	Reason for contact	Reason for Exclusion
Belman, 1996	Prospective cohort	No number of children delayed and not delayed or means and standard deviation of MDI and PDI in HIV+ and HIV negative children	Delivery of Email failed
<b>Blanchette et al, 2001. Toronto</b>	Cross sectional study	No number of children delayed and not delayed or means and standard deviation of MDI and PDI	Author did not respond
<b>Bobat, 2001. South Africa</b>	prospective, hospital-based, cohort study	Anthropometric outcomes presented in Z scores	Email delivery failed
<b>Bruck, 2001. Brazil</b>	Prospective Longitudinal cohort	Author not contacted	Study published by Tahan 2006 and included in the review
<b>Nozyce et al, 1994. USA</b>	Prospective cohort Study	Results presented in graphs and no means +SD	Author did not respond
Piazza et al, 1994. Italy	Prospective Cohort	Study in Italian	Author responded Italian study could not be translated to English.

**Appendix 4**

**Quality Assessment of Included Studies**

<b>New castle for cohort studies</b>			
<b>First author</b>	<b>Selection</b>	<b>Comparability</b>	<b>Outcome</b>
<b>Aylwald</b>	Recruited from inner city referral hospital, Exclusion criteria; Preterm's/premature infants excluded * Study group tested for HIV* Community controls* No neurological exam at entry	Matched with age pre terms excluded and iv and substance abuse interpreted.	Assessor blinded and BSID used* 2year follow up* LFTU with selective reporting. 172enrolled, 101, enrolled, 10 lost to follow up and 5 excluded.
<b>Total 7</b>	***	**	71??? **
<b>Boivin</b>	Recruited from a previous study and hospital records and author mentioned representativeness in community, exclusion criteria, sick children * Community controls used* No neurological exam at entry	Matched with age, gender, educational level of mother and socio economic status	examiners were blinded with K ABC* 2 year follow up* LTFU all participants analysed*
<b>Total 8</b>	Tested for HIV* ***	**	***
<b>Chase</b>	All participants enrolled at birth and recruitment of mothers during Pregnancy, Exclusion criteria multiple births and infants born to mothers already enrolled. * Controls from the same community * A neurological exam done at entry level* An HIV test was done*	Matched with age, socio economic status, and prenatal drug use, maternal educational level prematurity incorporated as covariate in the modeling process.	No blind assessment BSID 2 year follow up* 13 in HIV group died All children were analysed** Multivariate analyses done. <b>HIGH quality</b>
<b>Total 8</b>	****	**	**

<p><b>Drotar</b></p> <p><b>Total 8</b></p>	<p>Recruitment done during pregnancy and children enrolled at birth, exclusion preterm's *</p> <p>Randomised community controls *</p> <p>Gross neurologic impairments on physical examination were excluded*</p> <p>Study participants were tested for HIV*</p> <p>****</p>	<p>Matched with age and gender, maternal education level and only full term babies were enrolled.</p> <p>Stratifying group means for home and environment</p> <p><b>HIGH quality</b></p> <p>**</p>	<p>physicians blinded with BSID*</p> <p>2years follow up*</p> <p>56% died in HIV + and 1 in control group* 7% lost to follow up</p> <p>**</p>
<p><b>Fishkin</b></p> <p><b>Total 7</b></p>	<p>Represent a larger population of HIV infected children, *</p> <p>Community controls healthy children at child wellness centre*</p> <p>Medical records were reviewed for neurological development</p> <p>Study participants tested for HIV *</p> <p>***</p>	<p>Matched with age, gender, ethnicity, prenatal drug exposure.</p> <p>**</p>	<p>Data collector was blinded to WPPSI-R performance *</p> <p>No follow up statement</p> <p>13 children died by the time data was collected in the HIV +group but all children were analysed*</p> <p>**</p>
<p><b>Gay</b></p> <p><b>Total 8</b></p>	<p>Maternal recruitment during pregnancy*</p> <p>Community controls, Exclusion criteria maternal use of illicit drugs*</p> <p>Initial Neuro assessment as inclusion criteria*</p> <p>Participants tested for HIV*</p> <p>****</p>	<p>Matched by maternal prenatal substance exposure, ethnicity, socioeconomic Status (SES), and maternal separation and death.</p> <p>**</p>	<p>No blinding with BSID</p> <p>Follow up 2 years* (40.6% and 51.5% of the data for infected <b>and</b> uninfected infants, respectively),</p> <p>All children analysed*</p> <p>**</p>
<p><b>Knight</b></p> <p><b>Total 8</b></p>	<p>Retrospective study from referral hospital on children with development and neurological assessments *</p> <p>Community controls also referred to the hospital family based care*</p> <p>Retrospective study with two assessments 4 to 12 months apart</p> <p>Participants tested for HIV*</p>	<p>Matched by age, gender, prenatal drug exposure, ethnicity status</p>	<p>Psychologists were blinded with BSID*</p> <p>Two developmental tests 4 to 12 months apart*</p> <p>All children were analysed*</p>

	***	**	***
<b>Lindsey</b>	Maternal recruitment during pregnancy for Arv study, no children excluded* Community controls* Neurological assessment done at baseline* Participants tested for HIV*	Maternal ART exposure, maternal history of IV drug use, birth weight, educational level of the primary care giver**	No blinding with BSID* 3 months intervals for 24 months* 13% HIV – and 6% HIV + LTFU*
<b>Total 8</b>	****	Confounding factors- Univariate analysis <b>HIGH QUALITY**</b>	**
<b>Mc Grath</b>	Maternal recruitment during pregnancy, no children excluded * Community controls * No neurological assessment at baseline Participants tested for HIV baseline*	Participants were matched by socio economic status, age and gender, prematurity.  **	examiners were blinded with BSID* 6 months intervals for 18 months* 29% HIV- and 27% HIV+ LFTU Inconclusive results of LFTU. Author contacted **
<b>Total 7</b>	***		
<b>Miller</b>	Retrospective review of data from a referral hospital for children with history of HIV infection* Community controls(Seroreverters)* Birth weights taken* HIV tested and available on records*	matched by weight and gestation age	Birth weights extracted Length of follow up No loss to follow up* **
<b>Total 8</b>	****	**	*
<b>Msellati</b>	Maternal recruitment at birth and Community controls, plus exclusion criteria of children with indeterminate status** No initial neurological assessment Participants tested for HIV*	Matched with age and, prematurity and gestational age, Socio economic status. stratifying of confounding done** <b>HIGH QUALITY</b> **	physician blind to status with part of (Denver score and Illingworth's)* followed up for 2 years* cumulative mortality in HIV+ group was 58% by the end of 24months **
<b>Total 7</b>	***		
<b>Tahan</b>	Recruited at Paediatric Infectology and Neurology outpatient clinics of the	Matched with age The exclusion criteria	Denver and CAT/CLAMS*

<b>Total 8</b>	Clinical Hospital of UFPR, exclusion criteria of 2 or more normal neurological assessments* community controls* initial neurodevelopment as inclusion criteria* Participants tested for HIV* ****	were neurological complications, * *	7 years follow up* All children analysed*  ***
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<b>Quality Assessment ( cross sectional)</b>			
<b>Primary Author</b>	<b>Selection</b>	<b>Comparability</b>	<b>Exposure</b>
<b>Abubakar</b>  <b>Total 8</b>	Tested for HIV* Cases were obviously HIV positive children speaking the local language* Community controls who were randomly excluded* Controls defined as healthy and free from disease* ****	Matched by age, gender, socio economic status maternal education*  **	Examiners were blinded* Both groups assessed by kififi scale *  **
<b>Dobrova-Krol</b>  <b>Total 7</b>	HIV result available on records* Cases HIV positive children* Community controls* Controls defined as healthy and free of disease *	Matched on age, socioeconomic status , maternal age  **	No blinding (Snijders-Oomen Nonverbal Intelligence Test– Revised [SON–R]) k for both groups *
<b>Van Rie</b>	HIV-infected children were identified through a paediatric HIV care and treatment program- record linkage* obviously representative of HIV infected children, sick children excluded*	Matched with age and gender Clinical and anthropometric data, socioeconomic status	No blinding Both groups Assessed with BSID*

<p><b>Total 7</b></p>	<p>Community controls*                  Controls defined as absence of an illness that interferes with daily activities*                  *****</p>	<p>and health status of the parents were assessed enrolment.                  **</p>	<p>*</p>
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## Appendix 5

### Data Extraction of Included Studies

Abubakar et al., 2009

Cross sectional study: 1

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: method used: home visits, interviews	✓	
Relevant confounders described: Preterm birth, substance abuse during pregnancy, home and environment, age and disease stage	✓	
Method used for controlling for confounding At design stage: matching		✓
Variables on which subjects matched: Age At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		yes

### Data extraction

	Entire study	Intervention	Control
Number of participants identified	367	31	319
Number of participants: excluded/lost to follow-up		none	None
Number of participants included			
All participants accounted for?	yes ✓ no <input type="checkbox"/>		
Eligibility / inclusion / exclusion criteria		HIV positive aged 6 to 35months	HIV negative aged 6 to 35 months

### Characteristics of participants

Characteristic	Con	Exposed	Unexposed	Diff <sup>t</sup>
Age	✓	aged 6 to 35 months	6–35 months,	9 mo
Sex	✓	160:159	17: 14	



Living in home / institution	✓	Home	Home	
Rural / urban setting	✓	rural	Rural	
HAART or any Treatment		Not mentioned	Not mentioned	
Place of examinations	✓	Exams done @home	Exams done @home	
Substance abuse during pregnancy	✓	Not mentioned	Not mentioned	
Preterm delivery		Not mentioned	Not mentioned	
tested for HIV/ Healthy	✓	yes	No	

Aylwald et al., 1992

cohort Study: 2

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: questionnaire interviews and urine toxicology report	✓	
Relevant confounders described: IVI substance abuse, age, home environment, socioeconomic status	✓	
Method used for controlling for confounding		
At design stage: <span style="float: right;">matching</span>		✓
Variables on which subjects matched: Infants age, maternal education and age		
At analysis <span style="float: right;">ZV</span>		✓
stage: stratification		✓
multivariable regression		✓
propensity scores (matching)		✓
propensity scores (multivariable regression)		
Blinding: examiners were blinded		✓

**Data Extraction**

	Entire study	Intervention	Control
Number of participants identified	172		
Number of participants: excluded/lost to follow-up	10 + 5indefinite status	3	7
Number of participants included	96	12	45hiv +39 exposed
All participants accounted for?	yes ✓ no <input type="checkbox"/>		

Eligibility / inclusion / exclusion criteria	HIV positive	HIV negative
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**Characteristics of participants**

Characteristic	Con	HIV positive	HIV negative	Diff't?
Age	✓	Mean: 10.2months	Mean: 10.2months	
Sex: male: female	✓	7:12	24:45	
Living in home / institution (foster care)	✓	4:12	15:45	
Rural / urban setting	✓	urban	Urban	
Haart or any Treatment	✓	Not mentioned	Not mentioned	
Substance abuse during pregnancy	✓	8:12	41:45	
Preterm delivery	✓	Not mentioned	Not mentioned	
tested for HIV	✓	yes	No	

**Boivin et al., 1995**

**cohort, Study:3**

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: Home visits and evaluations	✓	
Relevant confounders described: socio economic status, confirmed HIV status, age	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Infants age, maternal education and age, mode of delivery	✓	<input type="checkbox"/>
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		yes

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	93	52	41
Number of participants: excluded/lost to follow-up	52	41	11
Number of participants included	41	11	15 sero and 15 neg
All participants accounted for?	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>		
Eligibility / inclusion / exclusion criteria		HIV positive, with a neurological assessment	HIV negative with a neurological assessment

### Characteristics of participants

Characteristic	Conf	HIV POSITIVE	HIV NEGATIVE	Diff*
Age	✓	54.8	54.8	hs
Sex: male: female		Not mentioned	Not mentioned	
Living in home / institution		Not mentioned	Not mentioned	
Rural / urban setting	✓	urban	Urban	
Exams done @ hospital	✓	yes	Yes	
Haart or any Treatment	✓	No Haart	No Treatment	
Substance abuse during pregnancy		Not mentioned	Not mentioned	
Preterm delivery (mean week gestation)		Not mentioned	Not mentioned	
tested for HIV/healthy	✓			

Chase et al., 2000

Cohort Study:4

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: interviews and questionnaires and urine toxicology test, prenatal history, ultrasound and physical examination.	✓	
Relevant confounders described: Age, ethnicity, gender, prenatal drug use, prematurity, socio economic status	✓	

Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Age, ethnicity, gender, prenatal drug exposure, prematurity, socio economic status	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression) List confounders controlled for under Data extraction, characteristics of participants: Prematurity, prenatal drug use	✓    ✓	
Blinding		NO

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	1016	191	825
Number of participants: excluded/lost to follow-up	595	114	485
Number of participants included	421	77	344
All participants accounted for?	yes ✓ no <input type="checkbox"/>		
Eligibility / inclusion / exclusion criteria		>3 neurological exams included	> 3 neurological exams included

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff <sup>a</sup>
Age: mean	✓	Birth	birth	
Sex: male: female	✓	41:36	173: 171	
Living in home / institution		Not mentioned	Not mentioned	
Rural / urban setting	✓	Urban	urban	
Hospital Assessments	✓	Yes	yes	
Haart or any Treatment		Not mentioned	Not mentioned	
Substance abuse during pregnancy	✓	55.8%	39.2%	
Preterm delivery (M & SD)	✓	22%	17%	

Tested for HIV/ Healthy	✓	Yes	yes	
Death	✓	13died 3 excluded	0	

**Dobrova-Krol et al., 2010**

**Cross sectional study: 5**

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: excluded children with fetal alcohol syndrome	✓	
Relevant confounders described: socio economic status, age, fetal alcohol syndrome		✓
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Infants socioeconomic status, maternal age, sex,	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		no

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	64	29	35
Number of participants: excluded/lost to follow-up	6	1	5
Number of participants included	58	28	30
All participants accounted for?	yes ✓ no <input type="checkbox"/>		
Eligibility / inclusion / exclusion criteria		HIV positive	HIV negative

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: mean		52.145	42.81	✓
Sex: male: female				
Living in home / institution	✓	16	13	
Rural / urban setting	✓	urban	urban	
Haart or any Treatment	✓	yes	No Haart	
Substance abuse during pregnancy	✓	Exclusion criteria	Exclusion criteria	
Preterm delivery (M & SD)	✓	Family: -1.15 (1.21) institution - 1.36 (0.56)	Family: -0.32 (0.99) institution-0.81 (0.61)	
tested for HIV/healthy	✓	yes	no	

**Drotar et al., 1997**

**Cohort Study: 6**

Assessment of how researchers dealt with confounding: Excluding preterm's,	yes	no
Method for <i>identifying</i> relevant confounders described: neurologic and physical exam, Assessment of home and environment	✓	
Relevant confounders described: Only full-term infants without significant birth complications or neurologic or genetic impairments based on newborn physical examination were enrolled	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Age, ethnicity, gender, prenatal drug exposure At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)	✓	
Comparing group means was used to assess the home environment	✓	
Blinding	yes	

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	436	79	Exposed;241 HIV- :116
Number of participants: excluded/lost to follow-up	26	18 deaths	7+1 deaths
Number of participants included	410	61	Exposed:234 HIV-:115
All participants accounted for?	yes no ✓		
Eligibility / inclusion / exclusion criteria		completed bailey exam	completed bailey exam

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: mean	✓	birth	Birth	
Sex: male: female	✓	32:29	62:53	
Living in home / institution		16	13	✓
Rural / urban setting	✓	urban	Urban	
Hospital Assessments	✓	Yes	Yes	
Haart or any Treatment	✓	No Haart	No treatment	
Substance abuse during pregnancy		Not mentioned	Not mentioned	
Preterm delivery (M & SD)	✓	Full term	Full term	
tested for HIV/ healthy	✓	Yes	No	

**Fishkin et al., 2000**

**Retrospective cohort Study: 7**

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: urine toxicology	✓	
Relevant confounders described: Age, ethnicity, gender, prenatal drug use	✓	
Method used for controlling for confounding At design stage: matching		

Variables on which subjects matched: Age, ethnicity, gender, prenatal drug exposure		
At analysis stage: stratification		✓
multivariable regression		✓
propensity scores (matching)		✓
propensity scores (multivariable regression)		✓
Blinding		no

**Data Extraction**

	Entire study	Intervention	Control
Number of participants identified	80	40	40
Number of participants: excluded/lost to follow-up	13	13deaths	0
Number of participants included	80	40	40
All participants accounted for?	Yes ✓ no □		
Eligibility / inclusion / exclusion criteria		HIV positive 3 to 5 years	HIV negative 3 till 5 years

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Di
Age: mean	✓	3 till 5	3 till 5	
Sex: male: female		Not mentioned	Not mentioned	
Living in home / institution		No stats	No stats	
Rural / urban setting		urban	Urban	
Hospital Assessment	✓	Yes	Yes	
Haart or any Treatment		Not mentioned	Not mentioned	
Substance abuse during pregnancy	✓	Matched	Matched	
Preterm delivery (M & SD)		Not mentioned	Not mentioned	
tested for HIV/ healthy	✓	Reviewed from files	No	



Gay et al., 1995

Cohort Study: 8

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: Urine toxicology test and questionnaire	✓	
Relevant confounders described: ethnicity, maternal SES, maternal prenatal drug use, maternal separation and death, and birth history were controlled	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Age, ethnicity, gender, prenatal drug exposure, prematurity, socio economic status	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		no

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	130	29	101
Number of participants: excluded/lost to follow-up	4	1	3
Number of participants included	126	28	98
All participants accounted for?	Yes ✓ no □		
Eligibility / inclusion / exclusion criteria		HIV positive non premature	HIV negative non premature

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: mean	✓	38.7	38.7	
Sex: male: female	✓	53.6: 46.4%	43.9:54.1	
Living in home / maternal separation/death	✓	7.1	8.2	

Rural / urban setting	✓	urban	Urban	
Hospital Assessment	✓	Hospital	Hospital	
Haart or any Treatment		n=13		✓
Substance abuse during pregnancy	✓	excluded	Excluded	
Preterm delivery gestation	✓	38.7	38.7	
tested for HIV	✓	Yes	Yes	

**Knight et al., 2000**

**Cohort Study:9**

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: questionnaire, Patients files	✓	
Relevant confounders described: child age, gender, substance abuse, were controlled	yes	✓
Method used for controlling for confounding: Age, gender, ethnicity, drug exposure At design stage: matching	✓	
Variables on which subjects matched: child age, gender		
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		Yes

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	45	20	25
Number of participants: excluded/lost to follow-up	0	0	0
Number of participants included	45	20	25
All participants accounted for?	yes ✓ no □		
Eligibility / inclusion / exclusion criteria		>2 neurological exams	>2 neurological exams

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age:	✓	3 till 30 mo	3 till 30 mo	
Sex: male: female				
Living in home / primary caretaker not biological mother		Not mentioned	Not mentioned	
Rural / urban setting	✓	Urban	urban	
Hospital Assessment	✓	Yes	Yes	
Haart or any Treatment		no data	No treatment	
Substance abuse during pregnancy	✓	14	16	
Preterm delivery mean : sd		Not mentioned	Not mentioned	
tested for HIV/Healthy	✓	Yes	yes	

**Lindsey et al., 2007**

**Cohort Study: 10**

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders: questionnaire, urine toxicology test	✓	
Relevant confounders described: ethnicity, maternal SES, maternal prenatal drug use, ART exposure and birth history were controlled	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Age, ethnicity, gender, prenatal drug exposure, prematurity, socio economic status	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓
List confounders controlled for under Data extraction, characteristics of participants: drug exposure, prematurity.		
Blinding		no

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	929	91	838
Number of participants: lost to follow-up		5 (6%)	107 (13%)
Number of participants included	929	91	838
All participants accounted for?	yes no✓		
Eligibility / inclusion / exclusion criteria		Perinatally HIV exposed	Perinatally HIV exposed

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: mean		<1 year	< 1 year	
Sex: male: female	✓	44:47	421:417	
Living in home / not staying with biological parent		5.1%	24.1%	✓
Rural / urban setting	✓	Urban	urban	
Hospital Assessment	✓	Yes	Yes	
Haart or any Treatment		On Haart	No treatment	✓
Substance abuse during pregnancy		19.25	5.5%	✓
Preterm delivery <2500g	✓	66.7%	82.8%	
tested for HIV		Yes	Yes	
Maternal ART exposure		46.5%	96.6%	

**Mc Grath et al., 2006**

**Cohort Study: 11**

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: files reviewed for birth history and maternal cd4	✓	
Relevant confounders described: maternal cd4 count and birth history were controlled		✓

Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Age, prematurity, socio economic status	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		yes

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	327	Not stated	Not stated
Number of participants: excluded/lost to follow-up	11%	27% died	29% died
Number of participants included	276	55	221
All participants accounted for?	yes no ✓		
Eligibility / inclusion / exclusion criteria		Bailey assessment, single delivery	Bailey assessment, single delivery
Blinding			Yes

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age:	✓	Birth till 18 months	Birth till 18 months	
Sex: male: female (167:160)				
Living in home / institution		Not mentioned	Not mentioned	
Rural / urban setting	✓	Urban	Urban	
Haart or any Treatment		Not mentioned	Not mentioned	
Substance abuse during pregnancy		Not mentioned	Not mentioned	
Preterm delivery (75:327)	✓			
tested for HIV	✓	Yes	Yes	

Miller et al., 1993

Cohort Study:12

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: Hospital records	✓	
Relevant confounders described: child cd4 count, prematurity, and ARV exposure were controlled	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Age, prematurity, socio economic status	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		no

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	71	52	37
Number of participants: excluded/lost to follow-up			
Number of participants included	71	52	37
All participants accounted for?	Yes ✓ no <input type="checkbox"/>		
Eligibility / inclusion / exclusion criteria		HIV +, receiving formula providing increased energy.	Exposed, receiving formula providing increased energy.

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: mean		12mo	19	✓
Sex: male: female (167:160)				
Living in home / institution		Not mentioned	Not mentioned	

Rural / urban setting	✓	Urban	Urban	
Hospital setting	✓	Yes	Yes	
Haart or any Treatment	✓	Excluded	Excluded	
Substance abuse during pregnancy		Not mentioned	Not mentioned	
Preterm delivery	✓	19	15	
tested for HIV	✓	Yes	Yes	

**Msellati et al., 1995**

**Cohort Study:13**

<b>Assessment of how researchers dealt with confounding</b>	<b>yes</b>	<b>no</b>
Method for <i>identifying</i> relevant confounders described: Hospital records, questionnaire	✓	
Relevant confounders described: child cd4 count, prematurity, maternal age and socio economic status, were controlled	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: Age, prematurity, socio economic status	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)	✓	
Analysis was stratified by birth weight for prematurity or low birth weight	✓	
Blinding		Yes

**Data extraction**

	<b>Entire study</b>	<b>Intervention</b>	<b>Control</b>
Number of participants identified	436	50	218
Number of participants: excluded/lost to follow-up	24deaths + 32 indeterminate	11 deaths	13 deaths

	status		
Number of participants included	436	50	218
All participants accounted for?	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>		
Eligibility / inclusion / exclusion criteria		HIV positive	HIV negative

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: mean	✓	Enrolled at birth	Enrolled at birth	
Sex: male: female				
Living in home / institution		Not mentioned	Not mentioned	
Rural / urban setting	✓	urban	Urban	
Hospital Assessment	✓	Yes	Yes	
Haart or any Treatment		No treatment	No treatment	
Substance abuse during pregnancy		Not mentioned	Not mentioned	
Preterm delivery	✓	35	29	
tested for HIV/ defined as healthy	✓	Yes	Yes	

Tahan et al., 2006

Cohort Study: 14

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: If yes, describe the method used: interviews, hospital records	✓	
Relevant confounders described: child age were controlled The exclusion criteria were neurological complications, such as neonatal meningitis, congenital toxoplasmosis or cytomegalovirus, hypoxic isquemic encephalopathy,	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: HIV status Normal neurologic examination and age	✓	



At analysis stage: stratification		✓
multivariable regression		✓
propensity scores (matching)		✓
propensity scores (multivariable regression)		✓
Blinding		Yes

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	172	88	84
Number of participants: excluded/lost to follow-up	24.4%		42
Number of participants included	172	88	84
All participants accounted for?	Yes ✓ no <input type="checkbox"/>		
Eligibility: <b>exclusion</b> criteria were neurological complications, such as neonatal, meningitis, congenital toxoplasmosis or cytomegalovirus, hypoxic isquemic encephalopathy.		HIV positive	HIV negative

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: mean	✓	1month till 36 mo	1 month till 36mo	
Sex: male: female		Not mentioned	Not mentioned	
Living in home / institution		Not mentioned	Not mentioned	
Rural / urban setting	✓	urban	Urban	
Hospital Assessment	✓	Yes	Yes	
Haart or any Treatment		No treatment	No treatment	
Substance abuse during pregnancy		Not mentioned	Not mentioned	
Preterm delivery		Not mentioned	Not mentioned	
Tested for HIV/ healthy	✓	Yes	Yes	
Maternal ART exposure		Not mentioned	Not mentioned	

Van Rie., 2009

Cross sectional Study: 15

Assessment of how researchers dealt with confounding	yes	no
Method for <i>identifying</i> relevant confounders described: Socioeconomic status was assessed by inquiring about access to running water, number of bedrooms, income, type of toilet, adequacy of income, and food.	✓	
Relevant confounders described: Clinical and anthropometric data, socioeconomic status, and health status of the parents were collected at enrolment.	✓	
Method used for controlling for confounding At design stage: matching Variables on which subjects matched: child age, gender	✓	
At analysis stage: stratification multivariable regression propensity scores (matching) propensity scores (multivariable regression)		✓ ✓ ✓ ✓
Blinding		no

**Data extraction**

	Entire study	Intervention	Control
Number of participants identified	160	35	35 Exposed and 90 HIV+
Number of participants: excluded/lost to follow-up	0	0	0
Number of participants included	160	35	90
All participants accounted for?	Yes ✓ no <input type="checkbox"/>		
Eligibility / inclusion / no exclusion criteria		HIV positive	HIV negative

**Characteristics of participants**

Characteristic	Con	HIV POSITIVE	HIV NEGATIVE	Diff
Age: median	✓	45.7	45.6	
Sex: male: female	✓	15:35	45:90	
Living in home / Orphaned		10	0	✓

Rural / urban setting		Urban	urban	
Hospital Assessment	✓	Yes	yes	
Haart or any Treatment		HAART naive	No treatment	
Substance abuse during pregnancy		Not mentioned	Not mentioned	
Preterm delivery		Not mentioned	Not mentioned	
Tested for HIV/ Healthy controls	✓	Yes	yes	
Maternal ART exposure		Not mentioned	Not mentioned	

## APPENDIX 6

### NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE: CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

#### Selection

- 1) Is the case definition adequate?
  - a) yes, with independent validation
  - b) yes, eg record linkage or based on self reports
  - c) no description
- 2) Representativeness of the cases
  - a) consecutive or obviously representative series of cases
  - b) potential for selection biases or not stated
- 3) Selection of Controls
  - a) community controls
  - b) hospital controls
  - c) no description
- 4) Definition of Controls
  - a) no history of disease (endpoint)
  - b) no description of source

#### Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis
  - a) study controls for \_\_\_\_\_ (Select the most important factor.)
  - b) study controls for any additional factor  (This criteria could be modified to indicate specific control for a second important factor.)

#### Exposure

- 1) Ascertainment of exposure
  - a) secure record (eg surgical records)
  - b) structured interview where blind to case/control status
  - c) interview not blinded to case/control status
  - d) written self report or medical record only
  - e) no description
- 2) Same method of ascertainment for cases and controls
  - a) yes

b) no

3) Non-Response rate

- a) same rate for both groups
- b) non respondents described
- c) rate different and no designation

**NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE: COHORT STUDIES**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

**Selection**

1) Representativeness of the exposed cohort

- a) truly representative of the average \_\_\_\_\_ (describe) in the community
- b) somewhat representative of the average \_\_\_\_\_ in the community
- c) selected group of users eg nurses, volunteers
- d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

- a) drawn from the same community as the exposed cohort
- b) drawn from a different source
- c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

- a) secure record (eg surgical records)
- b) structured interview
- c) written self report
- d) no description

4) Demonstration that outcome of interest was not present at start of study

- a) yes
- b) no

**Comparability**

1) Comparability of cohorts on the basis of the design or analysis

- a) study controls for \_\_\_\_\_ (select the most important factor)
- b) study controls for any additional factor  (This criteria could be modified to indicate specific control for a second important factor.)

**Outcome**

1) Assessment of outcome

- a) independent blind assessment
- b) record linkage
- c) self report
- d) no description

2) Was follow-up long enough for outcomes to occur

- a) yes (select an adequate follow up period for outcome of interest)
- b) no

3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for
- b) subjects lost to follow up unlikely to introduce bias - small number lost - > \_\_\_\_ % (select an adequate %) follow up, or description provided of those lost)
- c) follow up rate < \_\_\_\_% (select an adequate %) and no description of those lost
- d) no statement



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***TO WHOM IT MAY CONCERN***

This letter serves to confirm that the undersigned

**ILLONA ALTHAEA MEYER**

has proof-read and edited the document contained herein for language correctness.

(Ms IA Meyer)

SIGNED

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	A
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining	11





## PRISMA 2009 Checklist

		and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	14
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	14

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	15
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	16
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	19
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	22
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b)	24-28

		effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	<b>24-28</b>
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	<b>24-28</b>
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	<b>28-31</b>
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	32
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	34
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	35
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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## PRISMA 2009 Checklist

