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Abubakar, A.; van Baar, A.L.; van de Vijver, F.J.R.; Holding, P.; Newton, C.R.J.C.

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Paediatric HIV and neurodevelopment in sub-Saharan Africa: a systematic review

Amina Abubakar^{1,2}, Anneloes Van Baar², Fons J. R. Van de Vijver^{2,3}, Penny Holding^{1,4,5} and Charles R. J. C. Newton^{1,6,7}

1 Centre for Geographic Medicine Research – Coast, Kenya Medical Research Institute, Kilifi, Kenya

2 Tilburg University, Tilburg, The Netherlands

3 North-West University, Potchefstroom, South Africa

4 Case Western Reserve University, Cleveland, USA

5 African Mental Health Foundation, Nairobi, Kenya

6 Institute of Child Health, University College, London, UK

7 London School of Hygiene and Tropical Medicine, London, UK

Summary

OBJECTIVE To determine the degree of motor, cognitive, language and social-emotional impairment related to HIV infection in children living in sub-Saharan Africa (SSA).

METHODS Literature searches using MEDLINE and PsycINFO. Additionally, the reference lists of previous reviews were checked to ensure that all eligible studies were identified. Cohen's *d*, a measure of effect size, was computed to estimate the level of impairment.

RESULTS Six reports met the inclusion criteria. In infancy a consistent delay in motor development was observed with a median value of Cohen's *d* = 0.97 at 18 months, indicating a severe degree of impairment. Mental development showed a moderate delay at 18 months, with a median value *d* = 0.67. Language delay did not appear until 24 months of age, *d* = 0.91. Less clear findings occurred in older subjects.

CONCLUSION Although HIV has been shown to affect all domains of child functioning, motor development is the most apparent in terms of severity, early onset, and persistence across age groups. However, motor development has been the most widely assessed domain while language development has been less vigorously evaluated in SSA, hence an accurate quantitative estimate of the effect cannot yet be made.

keywords HIV, Africa, systematic review, neurodevelopment, children

Introduction

Approximately 80% of all HIV-1 positive children in the world live in sub-Saharan Africa (SSA) (UNAIDS 2006). The effect on mortality has been established, but the effect on the morbidity and neurodevelopment is not clear. Vertical transmission is the main mode of infection among young children (Wiktor *et al.* 1997). The mother-to-child transmission can occur *in utero*, at birth or through breastfeeding. The cumulative rates of transmission from the mother are 25–40%. Less than 10% of the infections are acquired *in utero*, about 10–20% at delivery while breastfeeding accounts for 10–20% of vertical infection (Dabis & Ekpini 2002). Acquisition of infection through breastfeeding is largely attributable to mixed feeding, where children who experience mixed feeding as opposed to exclusive breastfeeding during the first 6 months of life are

at a higher risk of vertical transmission (Coovadia & Bland 2007; Coovadia & Coutsooudis 2007).

In the past the prognosis for HIV infected children in SSA has been very poor with at least half dying before their second birthday (Newell *et al.* 2004) due to a lack of anti-retroviral (ARV) therapy. This is aggravated by poorly resourced and inaccessible health systems (Grant & De Cock 2001; Furber *et al.* 2004; Ter Kuile *et al.* 2004). Recent advances in the provision of Highly Active Anti-retroviral Treatment (HAART) are likely to decrease mortality rates, as has been observed in other parts of the world (de Martino *et al.* 2000; Gortmaker *et al.* 2001; Wong *et al.* 2004).

With the anticipated decrease in childhood mortality, the impact of HIV-associated disability will become increasingly important to practitioners and policy makers (World Health Organization 2005). This paper presents a

systematic and critical review of the literature on neurodevelopmental impairments associated with vertical HIV infection in children in SSA. The focus is on SSA-based studies because the constellation of risks (notably co-infections, undernutrition, and a poor support system) is different to other regions of the world (Grant & De Cock 2001), which may modify the outcome (Drotar *et al.* 1999).

The following questions are addressed:

- What is the degree of motor, cognitive, language and social-emotional impairment related to paediatric HIV in SSA?
- Which domains of functioning are most affected?
- What are the known risk factors?

Methods

Data sources and search strategy

Literature searches were carried out using MEDLINE (1980–December 2006) and PsycINFO (1887–December 2006). Additionally, we used the references cited in identified articles to find other publications. We administered a combined text word and MESH or subject heading to identify relevant papers. The search terms included ‘HIV infection’, ‘Child development’, ‘Neurobehavioral manifestations’, ‘Neurodevelopmental outcomes’, ‘Developmental impairments’, ‘Cognitive impairments’, ‘Language impairments’, and ‘Motor impairments’.

Study selection

The online abstracts of studies were reviewed and prints of eligible studies obtained. All reports were reviewed by the first author. Studies were included if they met the following criteria:

- Conducted in SSA;
- HIV infection was the risk factor studied;
- Children younger than 15 years, who acquired infections from their mothers;
- The study used controls or a psychological tool standardized in the study population;
- A developmental variable was the main outcome measure.

Data extraction

Data were extracted from the original sources by two of the authors (AA and CN) independently. Children were classified ‘infected’ if they had positive HIV antibody test older than 18 months or a polymerase chain reaction (PCR) test if they were younger than 18 months, and

‘uninfected’ if they were negative. They were considered ‘exposed’ if they were born to HIV-positive mothers but tested negative. Children were classified ‘unexposed’ if they were born to a HIV-negative mother.

Magnitude of impairment

The small sample size prohibited a full meta-analysis. Therefore, only Cohen’s *d*, the standardized difference between two means, was computed to estimate the magnitude of impairment; the cut-off values of small, moderate, and severe levels of impairment are 0.20, 0.50, and 0.80 (Cohen 1988).

Results

Overview of SSA-based studies

A total of six full-text articles presenting seven empirical studies could be used for further analysis (Figure 1), with the tests used are presented in Table 1, which also present a summary of the characteristics of the studies from SSA. The first study was conducted in Rwanda (Msellati *et al.* 1993), and assessed gross motor, fine motor, social-emotional, and language development. Neurological

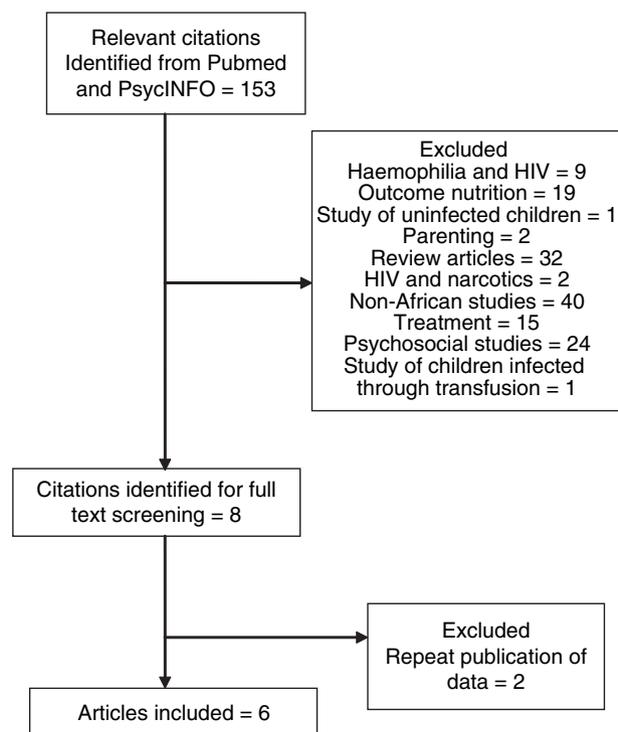


Figure 1 Flowchart of the study selection.

A. Abubakar *et al.* **Paediatric HIV in SSA****Table 1** Overview of studies from SSA

First author	Country of study	Sample	Age	Study design	Measurements	Changes	Validation	Domains studied
Msellati 1993	Rwanda	40+ 128– 186 c	6–24 months	Longitudinal	Self developed measure based on the Denver and Illingworth (Illingworth 1975)	N/A	N/R	Fine motor Gross motor Language Socio-emotional
Boivin 1995†	DRC	14+ 20– 18 c	6–24 months	Longitudinal	Denver Developmental Screening Test (Frankenburg <i>et al.</i> 1981, 1992)		N/R	Fine motor Gross motor Language Socio-emotional
Boivin 1995†	DRC	11+ 15– 15 c	3–6 years	Cross-sectional	Kauffman Assessment Battery for Children Early Childhood Screening Profiles	Restricted the range of sub-tests Excluded items	Comparison of the factor structure N/R	Cognition Motor Cognition Language Mental
Drotar 1997	Uganda	59+ 211– 107 c	6–24 months	Longitudinal	Bayley Scales of Infant Development-1 Fagan Test of Infant Intelligence (Fagan & Detterman 1992) Measures of infant-caregiver interactions Home Observations for the Measurement of the Environment	Exchange of objects and picture stimuli to fit the cultural setting N/R N/A Excluded sub-scales of the test	N/R N/R N/R Inter-rater reliability	Motor Mental Information processing
Peterson 1999	Uganda	10+ 50–	20–30 months	Cross-sectional	Bayley Scales of Infant Development-1 Measures of infant-caregiver interactions Mother-Child affect Infant Security of Attachment (Walter & Dean 1985)	Exchange test stimuli to fit cultural setting N/A N/A N/A	N/R N/R Inter-rater reliability N/R	Socio-emotional Infant affect Mother affect
Bagenda 2006	Uganda	28+ 42– 37 c	6–9 years	Cross-sectional	Kauffman Assessment Battery for Children WRAT-3	Restricted the range of sub-test N/R	N/R N/R	Cognition Motor Mental
McGrath 2006	Tanzania	55+ 221 c	6–18 months	Longitudinal	Bayley Scale of Infant Development	Exchange of test stimuli to fit the cultural setting	N/R	Motor Mental

N/A, not applicable; N/R, not reported; +, HIV positive; –, HIV negative; c, community controls.

†These studies are reported in a single publication.

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abnormality was assessed by a physician's judgment of the presence of signs of encephalopathy. A study conducted in the Democratic Republic of Congo (DRC) (Boivin *et al.* 1995) assessed gross motor, fine motor, language, and personal-social development among infants. In older children Boivin *et al.* (1995) administered a translation of the Kaufman-Assessment Battery for Children (K-ABC) (Kaufman & Kaufman 1983), measuring mental processing skills and the Early Childhood Screening Profile (ECSP) (Harrison *et al.* 1990), a screening tool to identify delays in motor, language and cognitive domains.

Drotar *et al.* (1997) studied effects of HIV infection on motor, mental and information processing abilities of Uganda children. Additionally, they administered an adapted version of the Home Observation of Measurement of the Environment (HOME) (Caldwell & Bradley 2001) which measures parenting behaviour and quality of stimulation in the home. A neurological exam was based on the Amiel-Tison scoring system (Amiel-Tison 1979). A subset of children from Drotar's studies (Peterson *et al.* 2001) was used to investigate the effects of maternal and child HIV-infection on attachment style and mother–infant interaction. When the children in Drotar's study reached school-age, Bagenda *et al.* (2006) undertook a long-term follow-up using the K-ABC, Wide Range Achievement Test–Third Edition (WRAT-3), which is a measure of reading, spelling and arithmetic achievement, and a neurological exam. A report on Tanzanian children (McGrath *et al.* 2006) studied the effect of timing of mother-to-child transmission on neurodevelopment with an adapted version of the Bayley Scales of Infant Development (BSID) (Bayley 1993).

Estimates of the rates and severity of impairment

Means and standard deviations were used to compute effect sizes in five studies (Msellati *et al.* 1993; Boivin *et al.* 1995; Drotar *et al.* 1997; Peterson *et al.* 2001; Bagenda *et al.* 2006). Effect sizes in the study by McGrath *et al.* (2006) were computed using means and standard error based on confidence intervals presented. The detailed diagrams of the means and confidence intervals in an infant study (Boivin *et al.* 1995) allowed estimation of means and standard error used to compute Cohen's *d*.

Neurological examination

In Rwanda the percentage of children with impaired scores at 6 months was 15%, rising to 40% by 18 months (Msellati *et al.* 1993). In Uganda a much higher rate was reported; 40% of the children were impaired at 6 months of age, and 56% at 18 months (Drotar *et al.* 1997). The infected survivors of this cohort showed no differences in

the frequency of neurological impairment compared to their uninfected peers (Bagenda *et al.* 2006).

Motor development

All studies that investigated motor development (Msellati *et al.* 1993; Boivin *et al.* 1995; Drotar *et al.* 1997; McGrath *et al.* 2006) report significant differences between HIV-infected children and controls. Table 2 shows that the difference in motor development appeared as early as 6 months of age, with a median effect size of $d = 0.61$ (moderate level of impairment), increasing by 18 months to a median effect size $d = 0.97$ (severe degree of impairment). In the only report of motor functioning in the school-age population, Boivin *et al.* (1995) also reported a significant difference between the infected and uninfected children (effect size $d = 1.38$, severe level of impairment).

Cognitive abilities

Children aged 24 months and younger were assessed with the mental development subscales of the BSID in two studies. Drotar *et al.* (1997) and McGrath *et al.* (2006) have investigated mental development in the HIV-infected group. The median effect size was $d = 0.39$ at 6 months, rising to $d = 0.67$ at 18 months (moderate impairment). However, Drotar *et al.* found no significant differences between the infected and uninfected children, with the Fagan Test of Infant Intelligence (Fagan & Detterman 1992). Two studies that evaluated general intellectual ability in children older than 2 years using the K-ABC found contradictory effects. Bagenda *et al.* reported no significant difference between HIV-positive children and controls in performance at 6–9 years of age, whereas Boivin *et al.* reported severe levels of impairment at 3–6 years of age in all aspects of functioning assessed by the K-ABC (Sequential processing: $d = 2.83$; simultaneous processing: $d = 2.16$; mental processing: $d = 2.84$; non-verbal skills: $d = 1.55$). Finally, the Early Childhood Screening Profile did not show significant differences between the groups (Boivin *et al.* 1995).

Language development

In two studies of infants (Msellati *et al.* 1993; Boivin *et al.* 1995) there were no significant differences in the language scores of children at 6 and 18 months of age. However, the Rwandan study (Msellati *et al.* 1993) reported a significant effect at 24 months of age ($d = 0.91$, severe impairment), whereas Boivin *et al.* (1995) did not find significant language deficits in a pre-school population.

Social, emotional and behavioural development

Two studies (Msellati *et al.* 1993; Boivin *et al.* 1995) have examined the social development of HIV-infected children

Table 2 Effect sizes for different domains in studies of young children

First author (Year)	Country	MDI at 6 months	MDI at 18 months	PDI at 6 months	PDI at 18 months	Language at 6 months	Language at 18 months	SE at 6 month	SE at 18 months
Examples of studies from developed countries†									
Alywards (1992)	USA		0.83		0.80				
Blanchette (2001)	Canada		0.82		1.09				
Chase (2000)‡	USA	0.51	0.85	0.64	0.77				
Condini (1997)	USA					Sig	Sig		
Llorente (2003)	USA		0.37		0.21				
McNeilly (1998)	USA					Sig	Sig		
Mellins (1994)	USA		0.35		0.75				
<i>Median</i>		0.51	0.82	0.64	0.76				
Studies in sub-Saharan Africa									
Boivin (1995)§	DRC			2.21	1.25	n/s	n/s	1.75	1.33
Drotar (1997)	Uganda	0.52	0.85	0.60	1.03				
McGrath (2006)	Tanzania	0.26	0.49	0.49	0.91				
Msellati (1993)§	Rwanda			0.61	0.77	n/s	n/s	0.54	0.46
<i>Median</i>		0.39	0.67	0.61	0.97			1.15	0.90

MDI, mental development index; PDI, psychomotor development Index; SE, social-emotional; Sig, significant difference; n/s, non-significant.

†Results of cross-sectional studies are reported as part of 18 months data.

‡Children assessed at 4 months of age.

§This study did not use the BSID (unlike the other studies reported in the table).

in SSA. Msellati *et al.* reported moderate effect sizes both at 6 and 18 months while Boivin *et al.* reported large effect sizes (see Table 2). Peterson *et al.* (2001) found that children who were HIV infected showed less secure attachment ($d = 0.59$) and less positive affect ($d = 1.08$).

Potential sources of variability

Contribution of social risk

Drotar *et al.* (1997) did not find any significant differences in parenting behaviour and home environment of HIV-positive, HIV-exposed and HIV-negative children in Uganda. They concluded that the developmental delays observed in the HIV group were independent of stimulation at home.

Contribution of biomedical risk

The only biomedical risk factor investigated is timing of infection. In Tanzania, McGrath *et al.* (2006) investigated the effects of timing of infection on neurodevelopmental outcomes in 11 children aged 6 months who tested HIV positive in the first 21 days of life. Significantly lower scores in the mental scales were observed among children testing positive in the first 21 days of life compared to the scores of those identified as late infected. At 6 months of age d was 0.65. The differences between the early infected and late infected children continued to increase to a d value of 1.27 by 18 months. In the motor scales, a small effect is

observed at 6 months of age ($d = 0.28$), which increased to a large effect ($d = 1.17$) by 18 months of age.

Discussion

We identified seven published studies of the effects of HIV infection on child growth and development in SSA, all carried out in countries in Eastern and Central Africa. This limited number has restricted the conclusions that can be drawn; yet, the data suggest that the magnitude of impairment in motor and mental development is similar to that observed in children in the West. The emergence and development of sensorimotor skills were found to be significantly compromised. Motor development was the most frequently measured area of functioning, providing consistent evidence of delay in HIV-positive children across all ages.

Contradictory results were found in the two studies of intellectual abilities in older children (Boivin *et al.* 1995; Bagenda *et al.* 2006). Differences in outcome may be attributable to sample characteristics, such as biomedical factors (e.g. viral load, CD4 count, timing of infection and disease stage), which are known to influence intellectual and psychological outcome (Smith *et al.* 2000, 2006). Both studies found that asymptomatic children had impaired growth patterns but details of other biomedical indicators were lacking. Furthermore, the potentially confounding effects of psychosocial factors experienced within the HIV

context such as suboptimal home environment, inadequate social support, and maternal depression (Brown & Lourie 2000; Stein *et al.* 2005) are not adequately addressed or reported.

The limited number of studies and the limitations of the instruments used in these studies have combined to provide an inadequate picture of the effect of HIV infection on language development in SSA. The use of limited instruments may have reduced the ability to detect language impairment (Glascoe *et al.* 1990). For instance, Msellati *et al.*'s (1993) measure had only three language items, and Boivin's language assessment included only six items from the Denver Developmental Screening Test (Frankenburg *et al.* 1992). Studies carried out in the rest of the world have consistently reported an impaired development in different domains of language functioning such as expressive and receptive language development (Concini *et al.* 1991; Wolters *et al.* 1995, 1997; Coplan *et al.* 1998; McNeilly 1998; McNeilly & Coleman 2000; Brouwers *et al.* 2001), even among infants and toddlers (18–30 months of age). Given the similarity of effects found in other functional areas, there is a strong possibility that after the application of appropriate measurement instruments, a similar effect on the language development of children in SSA will be observed.

While the significant effect of HIV on social-emotional development is consistent with reports from elsewhere in the world (Bose *et al.* 1994; Moss *et al.* 1994; Wolters *et al.* 1994; Mellins *et al.* 2003; Nozyce *et al.* 2006), the study reports lacked the detail required to compare the problems encountered by children in SSA to those elsewhere (Mellins *et al.* 2003). Furthermore, studies in SSA are yet to investigate factors that precipitate these effects. Evidence from the US (Mellins *et al.* 2003) indicates that the behavioural and emotional problems observed among HIV-infected children were related to social and demographic risk factors and not to HIV infection *per se*. Across the world the social context of many children with HIV involves poverty, a lack of resources and multiple family losses (Brown & Lourie 2000). Empirical evidence from the rest of the world indicates that biological and environmental risk factors interact to determine developmental outcomes (Sameroff & Fiese 1990; Bradley *et al.* 1993) although there is limited information on the relationship between familial factors and developmental outcomes in HIV infected families. One study reports that children with the most severe neurocognitive impairment had the least stimulating environment (Coscia *et al.* 2001). Only one study in Africa (Drotar *et al.* 1997) has investigated the home environment of HIV-infected children, which suggested that children who were HIV infected did not experience a less stimulating home environment than

uninfected children. The study did not investigate the potential interaction between environmental and biomedical risk, limiting the conclusions.

Only one study (McGrath *et al.* 2006) investigated the role of biomedical factors and timing of infection, on variability in neurodevelopmental outcomes. Early vertical infection was found to contribute to poorer developmental outcome, which replicates findings from the USA (Smith *et al.* 2000). More detailed investigations of other biomedical markers such as CD4 count, disease stage and nutritional status may identify children at highest risk of poor outcome, supporting the development of targeted follow-up. Such information in turn could help maximize the utilisation of limited resources in SSA.

The limited number of studies has restricted the ability to draw firm conclusions about the effect and magnitude of effect of HIV infection on developmental outcome of children growing up in SSA. Furthermore the lack of measures of childhood outcomes standardized for Africa; insufficiently sensitive measurement tools could potentially have masked true levels of group differences.

Despite these limitations this review indicates that the effects of HIV on children's development in SSA are likely to be similar to those found elsewhere. However, further study of vertically infected children in SSA is needed to describe the effect of HIV in this population in greater detail. The lack of relevant data from SSA is especially urgent for children above the age of two. We recommend that future studies administer an extensive battery of measures, as the effects of HIV on development appear to be wide ranging (Pulsifer & Aylward 1999; Rausch & Stover 2001). The variability in outcome found between studies requires further investigation. This information is needed for planning targeted interventions to meet the special needs of HIV-infected children in resource restricted settings such as that found in much of SSA.

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Corresponding Author Amina Abubakar, Department of Developmental, Clinical and Cross-Cultural Psychology, Tilburg University, PO Box 90153, 5000 LE Tilburg, The Netherlands. Tel.: +31 13 466 2870; Fax: +31 13 466 2067; E-mail: a.abubakarali@uvt.nl