Published in final edited form as:

New Dir Child Adolesc Dev. 2014 ; 2014(146): 23–41. doi:10.1002/cad.20071.

Biomedical Risk, Psychosocial Influences, and Developmental Outcomes: Lessons From the Pediatric HIV Population in Africa

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Abstract

Sub-Saharan Africa is home to millions of HIV-affected children. These children are likely to experience multiple developmental delays. In this chapter, I present data highlighting compromised neurobehavioral, mental health, and scholastic outcomes for children affected by HIV. Furthermore, I discuss biomedical factors (e.g., disease severity and nutritional status) that may exacerbate the adverse effects of HIV on childhood outcomes. I also present evidence on how psychosocial risk factors such as poor maternal mental health, orphanhood, and poverty may aggravate the effects of HIV. The concluding section of the chapter highlights conceptual and methodological refinements in research on the impact of HIV on child development in Sub-Saharan Africa.

Early exposure to ill health places children growing up in Sub-Saharan Africa (SSA) at an elevated risk of experiencing developmental and cognitive impairments (Mwaniki, Atieno, Lawn, & Newton, 2012). Impairments associated with diseases and conditions such as HIV (Abubakar, Van Baar, Van de Vijver, Holding, & Newton, 2008), malaria (Kihara, Carter, & Newton, 2006), malnutrition (Abubakar, 2013; Walker et al., 2007), and epilepsy (Aldenkamp & Bodde, 2005) contribute to low educational achievement, to low productivity in later life, and to the vicious cycle of poverty thus perpetuating social inequalities.

Elucidating the pathways between biomedical risk and childhood outcomes can help in identifying important points of intervention. These pathways are complicated by the presence of concurrent multiple risks. Although there is a growing body of literature illustrating the interconnectedness between biomedical and psychosocial risk factors in shaping developmental outcomes, many earlier studies have only attempted to quantify the burden of disease without adequately looking at the context.

Children in Africa face a myriad of medical challenges. However, I have restricted the scope of this chapter to pediatric HIV infection, with the expectation that lessons learned from the current evidence can be applied to the study of other childhood conditions. The chapter provides a critical evaluation of the existing literature, highlighting some of the most recent works with the aim of recommending future directions. In the first section, I review the evidence base on the impact of pediatric HIV infection. The second section scours the knowledge base to demonstrate the contribution of psychosocial risk factors to poor outcomes. I conclude the chapter with recommendations for refinement of conceptual and methodological models for studies oriented toward intervention.

Biomedical Risk Factors for Poor Childhood Outcomes: Focus on HIV

Children in Africa bear a disproportionate burden of the global HIV epidemic. It is estimated that 90% (approximately 2.3 million) of all HIV-positive children worldwide live in SSA (UNAIDS, 2012). A further 16 million have been orphaned by HIV/AIDS while an estimated 70–90 million are living in families affected by parental or caregiver HIV illness (Cluver, Orkin et al., 2013).

HIV has a propensity to invade both the central and peripheral nervous system. Autopsies on deceased HIV-positive patients have revealed that the brain was the second most frequently affected body organ (Hardy & Vance, 2009; Sullivan, 2009; Woods, Moore, Weber, & Grant, 2009). Consequently, structural brain damage, neurological complications, and consequent neurobehavioral manifestations are common in the HIV-infected population. The broad effects of HIV on the central nervous system mean that children living with HIV face multiple developmental impairments, although these adverse effects are not universal (Sherr, Croome, Parra-Castaneda, Bradshaw, & Herrero-Romero, 2014). Here, I highlight key findings and trends related to HIV-associated neurocognitive, mental health, and educational outcomes.

Neurobehavioral Outcomes

Childhood HIV has been related to adverse outcomes in motor, language, and cognitive domains (referred to here together as neurobehavioral outcomes). Studies of HIV-infected infants in Africa report impairments in motor, mental, and neurological functioning in the first two years of life (Drotar et al., 1997; Msellati et al., 1993). Multiple developmental delays have also been observed among preschool children. For instance, Van Rie, Mupuala, and Dow (2008), working in the Democratic Republic of Congo, observed that HIV-positive children suffered motor, language, and cognitive deficits. In a study involving 37 HIV-infected, 35 HIV-affected (see “Uninfected Children of HIV-Infected Parents” section), and 90 control children aged 18–72 months, it was observed that 60% of HIV-infected children had severe delay in cognitive function, 29% had severe delay in motor skills, 85% had delay in language expression, and 77% had delay in language comprehension, all at significantly higher rates compared with the control children. With one exception (Bagenda et al., 2006), all identified studies investigating neurocognitive outcomes among school-going children have observed delays (see Boivin et al., 2010; Ruel et al., 2012; Smith, Adnams, & Eley, 2008). The overall pattern of results indicates that children infected with HIV experience multiple developmental impairments early in life, and these impairments persist into late childhood and later life. Table 2.1 provides a summary of all the data that I was able to find on neurobehavioral outcomes of HIV infection in the African context.

Various factors may exacerbate the effects of HIV on neurobehavioral outcomes. Three of these factors that may be considered key are time of infection, disease severity, and nutritional status. In a study from Tanzania, McGrath et al. (2006) reported that children who are infected early (testing HIV positive at birth) were at a higher risk of experiencing developmental delays compared to those testing HIV-positive postnatally. Additionally, children at advanced stages of HIV infection (evaluated either by WHO disease staging or viral count) and those with poor nutritional status also performed much worse on measures

of neurocognitive outcomes (Abubakar, Holding, Newton, Van Baar, & Van de Vijver, 2009; Boivin et al., 2010; Potterton et al., 2009; Ruel et al., 2012).

The use of antiretrovirals (ARVs) improves clinical, immunological, and nutritional outcomes, leading to a significant decrease in mortality among infected children (Kabue et al., 2012). However, especially within the African context, there is limited evidence of the benefits of ARV use on neurobehavioral functioning. Results from the few studies in Africa examining the neurobehavioral impact of ARVs have not been consistent (see Table 2.1 for the pattern of results). The lack of positive effects may be related to various factors such as timing of treatment initiation and the lack of properly designed studies to investigate the impact of treatment. For instance, a study in South Africa involving 29 HIV-infected infants observed that the children on ARVs did not show improvement in their neurodevelopmental outcomes after initiation of treatment. However, they also did not show deterioration, something that was common in the pre-ARV use period (Whitehead, Potterton, & Coovadia, 2014). The authors concluded that their results could indicate that ARVs can stop further neurological damage, but may be unable to reverse the neurological damage experienced prior to treatment. The use of cross-sectional data or very short-term longitudinal data in the African-based studies on the neurocognitive outcomes of childhood HIV infection is a major limitation. As a result, little is known of developmental trajectories or of the long-term impact of treatment.

Mental Health

Research evidence on the social, emotional, and behavioral outcomes associated with being HIV positive during infancy and early childhood is scant, especially in the African context. Early work by scholars such as Msellati et al. (1993) and Boivin et al. (1995) has already documented impairments among HIV-positive children in their social and emotional functioning. Among older children the issue of mental health has been studied in greater detail. Here, mixed results have been reported, with some studies indicating poor outcomes while others did not observe any adverse effects of HIV. In an initial report, Menon, Glazebrook, Campain, and Ngoma (2007) looked at mental health outcomes of 127 HIV-infected adolescents from Zambia. They administered the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) and compared data from Zambia to British norms. Results indicated that the HIV-positive Zambian adolescents were at greater risk of mental health problems compared to the British sample. However, these comparisons should be made with caution as earlier cross-cultural studies discourage the use of norms from a different culture without adequately evaluating their validity. In subsequent reanalysis, Menon, Glazebrook, and Ngoma (2009) compared the data from the HIV-positive adolescents to a large sample of adolescents recruited from five Zambian high schools ($N=702$). The study observed that while the Zambian adolescents (both infected and uninfected) had higher scores on the SDQ compared to the British sample, affected and unaffected adolescents did not significantly differ from each other. This finding suggested that HIV-positive adolescents did not experience more mental health problems than their uninfected peers. In another study from Uganda, Musisi and Kinyanda (2009) reported high rates of psychiatric problems among HIV-positive adolescents. In their study, they found that 51.2% of the subjects had significant psychological distress (Self-Reporting Questionnaire: 25

scores of 6 or higher) while 17.1% had attempted suicide within the last 12 months. A high prevalence of psychiatric problems among HIV-infected adolescents has also been reported in a recent study in Kenya (Kamau, Kuria, Mathai, Atwoli, & Kangethe, 2012) in which 48% of the adolescents presented with psychiatric morbidity. This rate was much higher than the observed 20% in the general population. It must be noted, however, that the comparison was based on data collected more than 20 years ago, while the HIV data were more recent.

Various methodological shortfalls make it difficult to draw firm conclusions on the prevalence of mental health problems among HIV-infected children and adolescents in the African context. Such limitations include the use of measures not validated in context, with resultant poor psychometric properties. For instance, Menon et al. (2007) used the SDQ which yielded very low reliability levels (alphas ranging from 0.18 to 0.55) in the Zambian population. In addition, these studies did not control for potentially confounding factors (e.g., use of ARVs, home environment, and caregiver characteristics). Moreover, the lack of norms on mental health outcomes in the African context requires that studies be designed with carefully defined controls in order to adequately estimate the additional risk that being HIV-infected presents. There is a need for studies investigating the etiology, correlates, and patterns of mental health outcomes in children living with HIV.

Educational Outcomes

Relatively little is known of the educational outcomes of HIV-infected children. In one of the earliest studies of school-aged children, Bagenda et al. (2006) found no differences in achievement test scores between infected pupils and controls. However, a recent study by Devendra, Makawa, Kazembe, Calles, and Kuper (2013) in Malawi reported that HIV-infected children were more frequently absent from school, less likely to be in the appropriate grade level for their age, and less likely to achieve “above-average” school grades compared to their uninfected siblings. In a Kenyan study, Kamau et al. (2012) noted that 49% of the HIV-infected adolescents in their sample were at least two grades behind their peers. There is a need to carry out extensive investigations of the impact of perinatal HIV infection on educational outcomes.

Uninfected Children of HIV-Infected Parents

This group refers to children who were exposed to HIV prenatally, through maternal HIV infection, children for whom one or both parents is living with HIV, or children orphaned by an HIV-related illness. I refer to them as HIV-affected children. These children have been observed to experience various developmental delays, especially in the African context (Le Doaré, Bland, & Newell, 2012). Two potential pathways that may contribute to these delays have been hypothesized. The first is prenatal and early postnatal exposure to biomedical risk factors (Filteau, 2009). The second is the environmentally or socially mediated effect of growing up in a family affected by HIV. Children of parents who are HIV positive experience multiple stressors, such as parental illness and death, suboptimal parenting behaviors, stigma, destabilized home environment, and poor nutritional status (see Filteau, 2009, for a more detailed analysis of this issue). Given these circumstances, it is not surprising that studies in Africa report neurocognitive delays (Le Doaré et al., 2012), mental

health problems (Cluver & Gardner, 2006; Cluver, Gardner, & Operario, 2007), and poor educational outcomes (Guo, Li, & Sherr, 2012) for HIV-affected children.

HIV-affected children form the largest group of children adversely affected by the HIV pandemic. Understanding factors that put them at risk of poor developmental outcomes will inform the design of effective services aimed at enhancing their quality of life. Moreover, as this group shares the environmental risk experienced by HIV-infected children, they form an important control group for a study seeking to disentangle the associations between biomedical and psychosocial risk factors. Carefully designed studies comparing HIV-infected and HIV-affected children will go a long way in helping us understand the relative contribution of co-occurring risk factors.

The Clustering of Risk Factors

Worldwide, many children infected or affected by HIV are exposed to multiple risk environments—poverty, multiple losses through death, maternal depression, stigma, and suboptimal parenting behavior—all of which contribute to poor outcomes independent of HIV status (Stein et al., 2005). In the next section, I discuss some of the most salient risk factors that impact child development in the context of HIV.

Poverty

The relationship between socioeconomic status (SES) and HIV in Africa is not straightforward. HIV infection is by no means a disease of the poor. However, parental HIV infection may be related to poverty in various ways. First, parental HIV infection is likely to lead to prolonged periods of illness, lowered productivity, and extra medical-related expenses, contributing to lowered economic status for the family. Second, with improved treatment and care, HIV has changed from a fatal illness into a chronic one. A proper treatment regimen requires medication and adequate nutrition, among other factors. In extreme poverty situations, the lack of money to buy food or medication may exacerbate poor outcomes for children of people living with HIV, above and beyond the impact of HIV. Third, the environment of poverty, with the concomitant lack of clean water, poor hygiene, inadequate sanitation coupled with overcrowding, implies a higher risk of exposure to pathogens which increases the ease with which one is infected with opportunistic diseases. The resultant poor health in the infected parents contributes to suboptimal child development.

Maternal Psychosocial Functioning

Research indicates that people living with HIV are at a higher risk of poor mental health outcomes. For instance, Seth et al. (2014) in a study across three countries (Tanzania, Kenya, and Namibia) observed that up to 27% of the people living with HIV reported mild to severe depressive symptoms. The literature reveals that maternal mental health problems are likely to impact parenting behavior adversely, which in turn results in poor child function. A study involving 361 mother–child dyads in Tshwane, South Africa (Allen et al., 2014), investigated the relationships among mothers' psychological functioning, parenting behavior, and children's behavioral outcomes. The children were aged between 6 and 10

years. Using path analytic approaches, the authors reported that maternal depression was related to an increase in parenting stress and dysfunction in parent–child interactions, which in turn was associated with increased behavioral and emotional problems in children. The negative impact of compromised maternal psychosocial function within the context of HIV has also been reported among HIV-infected children. In a study of 119 children aged 1–5 years, Busman, Page, Oka, Giordani, and Boivin (2013) observed the caregiving context and found that the quality of the home environment was associated with externalizing behavioral problems among HIV-positive children.

Orphanhood

HIV-related orphanhood contributes to poor developmental, educational, and mental health outcomes. A study in Kenya involving 325 adolescents found that orphans experienced poorer mental health, had less social support, and fewer material resources (Puffer et al., 2012). Unfortunately, as the negative effects of HIV orphanhood are not transient, mental health conditions of HIV-orphaned children continue to be compromised as demonstrated through follow-up studies. A four-year longitudinal study of 1,021 South African children showed that AIDS-orphaned children had higher depression, anxiety, and posttraumatic stress disorder (PTSD) scores at both baseline and follow-up when compared with nonorphans and children orphaned through other reasons (Cluver, Orkin, Gardner, & Boyes, 2012). These effects remained even after controlling for background factors such as SES and age.

Stigma

HIV-related stigma is highly prevalent in many African countries and is experienced in various forms including abuse, discrimination, and exclusion. In a longitudinal study covering five African countries, up to 84% of people living with HIV reported having experienced at least one stigmatizing event in the past one year at baseline (Holzemer et al., 2009). At the 12-month follow-up, this figure declined to 65%, still considered a very high percentage. In the same study, up to 80% of nurses had observed at least one stigmatizing event against HIV-positive patients during the past one year; this figure increased to 84% during the follow-up period (12 months later; Holzemer et al., 2009).

HIV-related stigma adversely influences the quality of life of people living with HIV (Herrmann et al., 2013; Li et al., 2011). It also limits participation in social, economic, and cultural activities, as well as access to health services. These factors are likely to lead to suboptimal parenting behavior for adults who are parents, resulting in adverse outcomes for their children. Thus, parental perceived or experienced stigma has a negative influence on child adjustment.

Stigma affects HIV-infected and HIV-affected children both directly and indirectly. For instance, Boyes and Cluver (2013) reported higher levels of perceived stigma, anxiety, and depression among HIV/AIDS orphans. The results of a path analysis showed that orphanhood was not directly related to poor mental health; rather, stigma mediated the relationship between orphanhood and psychological adjustment. The indirect effects of

stigma on child development are seen in the manner in which parental stigma impacts parental childrearing abilities.

In summary, children who are HIV infected or affected experience developmental delays which may be related to biomedical, psychosocial risk factors, or a combination. How do we intervene to enhance psychosocial development and quality of life most effectively? Which are the most meaningful points of intervention? Where can we make the most impact to ensure that HIV-infected and HIV-affected children do *not just survive but thrive*? The available evidence provides a lot of information but major gaps still exist. Further refinement of both conceptual and methodological approaches will ensure that a strong evidence base guides intervention.

Future Directions

Compared with the literature from other parts of the world which carry a smaller disease burden, the study of the effects of pediatric HIV in Africa is relatively limited. Nevertheless, there are many important lessons to be learned. From the literature reviewed here, it is evident that we have gathered knowledge on the effects of HIV on various domains, on the biomedical factors that contribute to these adverse effects, and on the psychosocial influences that are likely to exacerbate the negative effects. However, current efforts on refining conceptual and methodological models should continue to guide the field in the adoption of data collection methods.

The need for this refinement arises for two reasons. First, as illustrated in Table 2.1, many studies on the impact of HIV infection on children have focused on the potential contribution of biomedical mediators (e.g., disease staging) while ignoring psychosocial issues. On the other hand, the literature on psychosocial risk has been strongly influenced by studies on HIV-affected children. There is a need for more work looking at these areas concurrently so as to gain a good understanding of factors contributing to poor outcomes in this population. Understanding factors that may contribute to poor outcomes among HIV-affected children is important since there is wide variability in outcomes, with some of these children experiencing developmental delays while others do not (Sherr et al., 2014).

Refining Conceptual Models

As earlier noted, children from families living with HIV are most likely to live in multiple risk environments. Given the interrelationship between these risk factors, a study design encompassing the conjoint and interactive effects among these risks will be considerably robust. Recent efforts at modeling data on health outcomes among HIV-positive children clearly illustrate the need to look at interactions among risk factors. For instance, a study by Cluver, Boyes, Orkin, and Sherr (2013) aimed at identifying children at the highest risk of negative health effects in the context of HIV noted that when family AIDS and poverty coexisted, children were placed at the highest risk of poor outcomes. Such studies on the interaction or additive effects of risk factors go a long way in elucidating the mechanisms through which a biomedical risk factor contributes to compromised childhood outcomes. However, the majority of recent modeling data has been based on studies of orphans. Consequently, the interaction between biomedical and psychosocial risk factors has hardly

been studied. Complex modeling and longitudinal analyses to examine the association between biomedical and psychosocial risk factors would yield useful insights.

Path analytic approaches using structural equation modeling where mediated and moderated effects can be examined provide state-of-the-art ways of interpreting the contribution of biomedical and psychosocial risk factors in shaping outcomes. Mediational models attempt to clarify the relationship between an independent (variable A) and a dependent variable (variable B) through a third variable. An alternative conceptualization postulates moderator effects. Moderation analysis examines if the relationship between an independent and a dependent variable changes when conditions vary. For instance, in HIV-related studies, one may want to investigate how the presence of a caregiver who is supportive, uses adequate parenting strategies, and does not experience stigma improves neurodevelopmental outcomes for children compared to conditions where psychosocial environments are compromised. Does the psychosocial factor of caregiving quality merely serve to attenuate or intensify the neurodevelopmental outcomes of infection (moderation), or does it actually feature as a step in the causal chain between biological factors and neurodevelopmental outcomes (mediation)?

Multilevel Model—Deducing from the reviewed literature it is clear that the impact of HIV varies at different ecological levels. Complex modeling has to take into consideration the numerous ecological levels in which a child operates and how they can influence development. Guided by the theoretical underpinnings of bioecological (Bronfenbrenner, 1979) and transactional (Sameroff, 2009) models of human development, it can be hypothesized that the (neurodevelopmental, educational, and mental health) outcomes of HIV-infected and HIV-affected children will result from the interaction between individual characteristics and factors at play within the family, school, health centers, neighborhood, and even the country (since country-level policies may influence access to care services and the degree of overt stigma). For instance, how well an HIV-infected child performs in school may be partially determined by individual characteristics (e.g., coping styles, personality, and social skills), disease factors (level of disease progression and neurological involvement), household characteristics (familial SES and parental investment in the child's education), and school characteristics (stigma experience, levels of support, and inclusion vs. exclusion). Large-scale studies using multilevel approaches to evaluate data are urgently needed as insights on the influence of context on child development may provide information on useful points of intervention.

Refining Methodology

In addition to generating more data, research on the pediatric HIV population in Africa needs to build on past experience by adopting new, more precise methods, including appropriately standardized instruments and longitudinal inquiries.

Using the Right Tools to Evaluate Risk and Outcomes—One of the most significant problems in quantifying the real burden of disease in Africa is a lack of adequately standardized tools (Holding et al., 2003; Kammerer, Isquith, & Lundy, 2013; Orkin, Boyes, Cluver, & Zhang, 2014; see Chapter 5 by Matafwali & Serpell for further

discussion of this topic). In addition to traditional paper and pencil approaches, neurological functioning can be assessed with neurophysiological measures such as magnetic resonance imaging, event-related potentials (ERPs), electroencephalography, and eye-tracking techniques. In Kilifi, Kenya, there has been work showing the efficacy of using ERPs in the study of the cognitive impact of infectious diseases, for example, in the study of the impact of malaria and meningitis (Kihara, de Haan, Garrashi, Neville, & Newton, 2008; Kihara et al., 2012). The expansion of technology that allows for relatively low cost, mobile data collection makes it feasible to use these methods to describe neurocognitive outcomes and biomarkers in resource-constrained environments (Bosl, 2012). Moving toward these new technologies allows the study of a greater range of outcomes and helps elucidate the structural correlates of behavioral manifestations.

Longitudinal Approaches—A significant proportion of the evidence on the impact of HIV on child development is derived from cross-sectional studies and a small number of short-term longitudinal studies. For this reason, we know little of developmental trajectories and causal pathways among this population. Many questions on the effects of HIV or exposure remain unanswered. For instance, we do not know to what extent cognitive delays impact educational outcomes. How do cognitive impairments impact health-seeking behavior, risk-taking behavior, and other important life skills? To gain a good understanding of these issues there is a need for longitudinal studies. The description of developmental trajectories across a long period of time allows for a better description of causal pathways. Additionally, the effects of HIV and its manifestations may change as children grow older. Therefore, there is a need for a lifespan approach. For instance, the major concerns for children may relate to schooling and peer relationships during middle childhood. In adolescence, the concerns relate to risk-taking sexual behavior, dating, reproductive health choices, and taking responsibility for managing their health conditions.

Concluding Remarks

This chapter attempts to highlight the need to further refine the methodological and conceptual models to be used in examining the impact of HIV on child development. The use of sophisticated conceptual and methodological models has a two-fold benefit. First, within the unique constellation of risks and resources in the local context, Africa can benefit from the existing wealth of knowledge, tools, and scales to develop her own tools to address urgent developmental needs and identify the most meaningful points of intervention. Second, studies from Africa can provide a unique perspective on risk factors and sources of resilience, given the multitude of cultural groups, rapid urbanization coexisting with rural traditional settings, rapid economic change, and demographic transitions. Such a context allows the testing of bioecological models of development to confirm their basic assumptions and make appropriate modifications and additions. Through this, we can answer the immediate needs of the larger African population, as well provide an opportunity for Africa both to learn and to expand the knowledge base on risk factors. I focused on the pediatric HIV to draw a model which allows child development psychologists to examine the complex associations among various risk factors. However, it is hoped that the lessons

learned from the field of HIV can be transferred to other fields of study where biomedical risk interacts with psychosocial risk.

Acknowledgments

This chapter is published with the permission of the director of KEMRI. Amina Abubakar is supported by University of Oxford Tropical Network Fund, Wellcome Trust grant 092654/Z/10/A, and the Change Fellowship (funds provided by International Union of Psychological Science, National Research Foundation, and the Jacobs Foundation). I would like to acknowledge Fons Van de Vijver, Ype Poortinga, Amin Hassan, and Patricia Kitsao-Wekulo for providing valuable feedback on an earlier version of this chapter.

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Table 2.1
Summary of Studies Investigating Neurocognitive Outcomes Among HIV-Infected Children in Africa

Author	Year	Country	Sample ^a	Age	ARV	Design	Tools	Key Findings	Psychosocial Aspects
Msellati et al.	1993	Rwanda	43 I 133 E 193 C	Birth to 24 months	No	LG	Local tool	Multiple delays. 12.5% delayed at 6 months, 20% at 18 and 9% at 24 months.	None
Boivin et al. ^b	1995	DRC	14 I 20 E 16 C	3–18 months	No	LG	DDST	Delays in multiple developmental domains.	None
Boivin et al. ^b	1995	DRC	11 I 15 E 15 C	>2 yrs	No	CS	K-ABC ECSP	Multiple developmental delays.	None
Drotar et al.	1997, 1999	Uganda	59 I 211 E 107 C	Birth to 24 months	No	LG	BSID FTII HOME	Delays in motor and cognitive domains, none in information processing.	No difference in quality of home of HIV positive and controls
Bagenda et al.	2006	Uganda	28 I 42 E 37 C	6–12 years	No	CS	K-ABC WRAT	No significant delay or impairment was reported.	None
McGrath et al.	2006	Tanzania	327 I	6–18 months	No	LG	BSID-II	Early infected performed worse than later infected.	None
Baillieu & Potterton	2008	SA	40 I	18–30 months	No	CS	BSID-II	85% gross motor and 82% language delay	None
Smith et al.	2008	SA	39 I	14–106 months	Yes	LG	GMDS TROG DAP VMI/V P/ RCPM	Developmental delays observed. No change in status six months into ARV treatment.	None
Van Rie et al.	2008, 2009	DRC	35 I 35 E 90 C	18–72 months	Yes	LG	BSID-II PDMS SON	Developmental delays in infected children. After one year of medical care, HIV-infected children achieved mean motor and cognitive scores that were similar to HIV-uninfected and affected children although lower compared with control children.	None
Abubakar et al.	2009	Kenya	31 I 17 E 319 C	6–35 months	No	CS	KDI	Motor impairments. Performance worsened by disease progression and nutritional deficits.	None
Ferguson & Jelsma	2009	SA	51 I 35 C	6–32 months	34 out of 51	CS	BSID-II	66.7% of the HIV-infected children experienced motor impairments compared to 5.7% of the controls. No difference in performance between those on ARVs and those who are not.	None

Author	Year	Country	Sample ^a	Age	ARV	Design	Tools	Key Findings	Psychosocial Aspects
Boivin et al.	2010	Uganda	102 I	6–12 years	No	CS	KABC TOVA BOT-2	HIV clade influenced neurocognitive outcome, children with subtype A performing worse than those with subtype D.	None
Kandawasvika et al.	2011	Zimbabwe	65 I 188 E 287 C	Birth to 12 months	Yes	LG	BINS	HIV-infected children twice at risk of impairment; this effect becomes nonsignificant when you take into consideration other risk factors.	Levels of family income predictive of neurodevelopmental impairments
Jelsma, Davids, & Ferguson	2011	SA	23 I 21 E	30–59 months	Yes	CS	PDMS II	Motor delays (Cohen $d = 1.450$).	Residence in a foster home a predictor of outcomes
Lowick, Sawry, & Meyers	2012	SA	30 I 30 E	5–6 years	Yes	CS	GMDS-R	90% of HIV-positive children and 76% of controls developmentally delayed.	None
Ruel et al.	2012	Uganda	93 I 106 E	6–12 years	No	CS	KABC TOVA BOT-2	Multiple cognitive and motor impairments. Performance worsens with advanced disease staging.	HIV positive from lower SES but same scores on HOME
Hoare et al.	2012	SA	24 I	8–12 years	No	CS	WASI Imaging	Asymptomatic HIV-positive children had poorer neurocognitive outcomes compared to controls. Indicators of imaging showed poor outcomes. Strong correlation between imaging results and neurodevelopmental outcomes.	None
Laughton et al.	2012	SA	92 I 24 E 34 C	10–16 months	Some	CS	GMDS	Children who received ARVs early performed better than those initiated to ARVs later.	None
Boyede et al.	2013a, 2013b, 2013c	Nigeria	69 I 69 E	6–15 years	56% on ARV	CS	RPM	HIV positive delayed (Cohen d of 0.76). Those on ARVs better than those not on ARVs.	SES and maternal education influenced cognitive outcomes
Whitehead et al.	2014	SA	27 I	Six months	Yes	LG	BSID-II	At baseline 48.1% cognitive impairment, 51.8% language in the HIV positive group.	None
Kandawasvika et al.	2014	Zimbabwe	32 I 121 E 153 C	6–8 years	30% on ARV	CS	MSCA	No difference in performance except on perceptual tasks.	Cognitive impairments associated with caregiver unemployment, parental loss, and undernutrition

^aLongitudinal study, we report sample sizes at baseline.

^bThis chapter reported two different studies so we separated them in this report.

Design. LG: longitudinal; CS: cross-sectional.

Conditions. I: HIV infected; E: HIV exposed; C: community controls/HIV unexposed.

Locations. DRC: Democratic Republic of Congo formerly known as Zaire; SA: South Africa.

Instruments. DDST: Denver Developmental Screening Tool; BSID: Bayley's Scales for Infant Developmental; FTII: Fagan Test of Infant Intelligence; K-ABC: Kauffman Assessment Battery for Children; WRAT: Wide Range Achievement Test; KDI: Kilifi Development Inventory; GMDS-R: Griffiths Mental Developmental Scales-Revised; PDMS II: Peabody Development Motor Scale II; RPM: Raven's Progressive Matrices; BINS: Bayley Infant Neurodevelopmental Screener; TROG: Test for Reception of Grammar; DAP VMI/VP/Beery-Buktenica developmental tests for visual motor integration (VMI), visual perception (VP), and motor coordination (MC); MSCA: McCarthy Scales of Children's Abilities.