

# The Effect of HIV on Developmental Milestones in Children

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## Abstract

Development indicates maturation of functions; it is a continuous process starting in utero and progresses in an orderly manner until maturity. Both growth and development are closely related hence factors affecting one, also tend to affect the other. The Central Statistical Office's Living Conditions Survey of 2010 in Zambia indicated that amongst children aged between 3 to 59 months which is just under 6 years 48.3% of the children in the rural areas of Zambia were stunted and 42.3% were stunted in the urban areas with an average stunted rate of 46.7% overall in the whole country. The first 24 months of life technically denotes the infancy period. It is a time when a child's brain undergoes rapid development. During this phase, a child attains several milestones relating to motor, cognitive and behavioral development. This is a very sensitive period whereby any slight disruption to the process can negatively result into growth failure in terms of both motor and cognitive development. HIV has been linked to a wide range of developmental challenges such as cognitive development stagnation, neurological problems, learning difficulties and speech and language problems. Though it is difficult to isolate its singular effect on the neurological status of children infected with it, research has established that 90% of the HIV positive children have neurological problems. HIV is a serious health concern in Zambia, this paper highlights literature in this area and discusses the impact of HIV on the developmental milestones of children and makes a comparison to the developmental milestones of children who are HIV negative.

**Keywords:** HIV; Children; Developmental milestones; Neurocognitive development; Zambia

## Background

According to the World Health Organization, Department of HIV and AIDS, an estimated 3.4 million children are living with HIV worldwide, out of which 90% live in Sub-Saharan Africa [1]. In 2011 alone, 330,000 children worldwide acquired HIV; still 90% of these infections were recorded in Sub-Saharan Africa [2]. Many lives of children continue to be exposed to HIV due to the global prevalence of HIV infection in women. In sub-Saharan Africa, 58 % of the people living with HIV are women [3]. The 2007 Zambia Demographic Health Survey reports that about 16.1% of women aged 15 and 49 years were infected in 2007 [4]. As can be noted this is a child-bearing age group which is usually the most sexually active [5].

HIV in women easily finds its way in their infants through mother-to-child transmission (MTCT). In most cases, children acquire HIV through what would otherwise be preventable means such as during pregnancy, birth and breastfeeding. These are preventable modes in that vertical transmission can be avoided through the use of ART prophylaxes, caesarian birth and adoption of safe alternatives to breast milk [6]. Since more than half of all child births in Zambia do not take place in health facilities [7], prevention of MTCT remains a huge challenge. As long as this sad situation remains unattended to, any increase in the number of HIV positive women will directly translate into an increase in the number of children born with HIV.

In trying to deal with the problem of MTCT during pregnancy and labor, a number of WHO-recommended regimens are often used. Most recently, combination therapy with highly active antiretroviral therapy (HAART) has gained wide usage in the management of HIV in pregnant women [8]. Nevertheless, much as vertical transmission of HIV may be reduced through ART [9], the breastfeeding mode still remains a very high-risk transmission mode [10].

## Growth and development of infants and young children with and without HIV infection in the first two years of life

**The complex milieu for normal growth and development:** The

physical, behavioural and mental development of infants and young children is structured around the family environment, parenting style, communication and relationships within the family, mainly among the parents and or other siblings. The immediate family therefore determines the pattern of growth and development of the infant [11].

Growth represents a net increase in the size or mass of tissues. It is largely attributed to the multiplication of cells and increase in the intracellular substance, organs grows in size. Development on the other hand indicates maturation of functions. It is a continuous process starting in utero and progressing in an orderly manner until maturity. Both growth and development are closely related hence factors affecting one, also tend to affect the other [12].

In the prenatal period maternal and fetal factors contribute to interruptions in growth and development. The pregnant woman needs to maintain good health in order to maximize the opportunity of good health for her unborn baby. If the mother for instance does not eat well, or does not supplement her diet with folate, she may increase the chance of her baby being born with a neural tube defect such as spina bifida. She herself will be stressed and may also have anemia. Similarly infections such as toxoplasmosis, rubella, cytomegalovirus, Herpes simplex and Human immune deficiency (HIV) can cross through the placental barrier to the baby resulting in infection by the same organisms. Disease in the infant has been shown over and over again to demonstrate an arrest in development [11,12].

Growth during the postnatal period is determined by genetic

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potential in addition to environmental effects. Tall or short stature may be genetic or due to chromosomal defects like Down's syndrome which manifests as shortness or Klinefelter's syndrome which manifests with tall stature, among known signs [13].

The Central Statistical Office's Living Conditions Survey of 2010 indicated that amongst children aged between 3 to 59 months which is just under 6 years, 48.3% of the children in the rural areas of Zambia were stunted and 42.3% were stunted in the urban areas with an average stunted rate of 46.7% overall in the whole country. 14.2% of the same category of children was underweight in the rural areas where as 10.8% were underweight in the urban areas and the country average of the stunted children was 13.3%. In terms of the children who were considered to be wasted, 6.4% were in the rural areas, 4.9% were in the urban areas where as the national average was 6%. Figure 1 clearly shows the alarming percentages of stunted children indicating unfavorable height, unacceptable percentages of the underweight and quite high levels of those who were wasted. These figures suggest that the nutritional status of the children in Zambia is not good and the observable status of being stunted, underweight and wasting away it can be argued has some effects on the children's cognitive development because it is well known that nutrition especially in the first four years is critical to the normal progression of cognitive development in childhood (Figure 2).

The Zambia Demographic and Health Survey of 2013/2014 has given figure for a 22 year period trend from 1992 to 2014 of the nutritional status of under five children. The figures show that 46% of the under five children were stunted in 1992, 49% were stunted in 1996 peaking to 53% in 2001/2002 tapering off to 45% in 2007 and dropping

to the lowest of 40% in 2013/2014. In the same period 21% under five children were underweight in 1992, 19% were underweight in 1996, 2001/2002 recorded the highest percentage of 23% and both 2007 and 2013/2014 periods recorded underweight rates of 15%. In terms of Wasted Percentages the whole 22 year period recorded rates of 6% or lower. Just like for the rural urban differentials of the 2010 figures the 22 year trend percentages for stunted children are alarmingly high in all the selected period points, the underweight percentages for the under five children are too high and the wasted children's percentage of about 5 percent for each selected time point is also unacceptable. It is clear from the analysis of the trends that although there have been some gains made in the improvement of the children's nutritional status the battle is not being won because the stunted and underweight under five aged children remains too high.

A myriad of external factors like socioeconomic levels, poverty, emotional deprivation, cultural influence may all affect growth and development of children. Protein energy malnutrition will cause anemia and vitamin deficiency states. The same under nourished children are also prone to infections manifesting as persistent or recurrent diarrhea, chest infections and systemic or parasitic infections [11].

The detection of children with developmental and behavioral problems that are subtle is a challenge as most are only detected at school entrance. Opportunities for early intervention tend to be missed.

**Neurocognitive milestones in infants without HIV infection:**

The first 24 months of life technically denotes the infancy period. It is a time when a child's brain undergoes rapid development. During this phase, a child attains several milestones relating to motor, cognitive and behavioural development. This is a very sensitive period where any

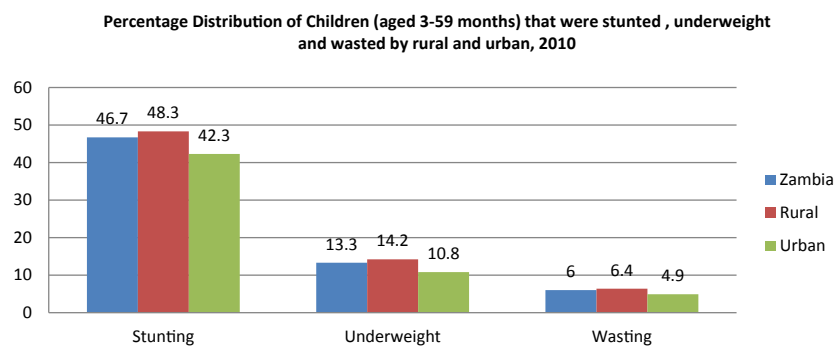


Figure 1: Percentage distribution of children (aged 3-59 months) that were Stunted, Underweight and Wasted by Rural and Urban, 2010. Source: CSO, Living Conditions and Monitoring Survey, 2010.

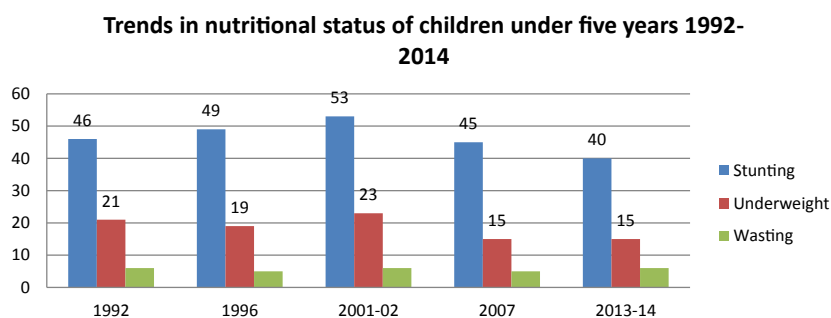


Figure2: Trends in nutritional status of Under Five children: 1992-2014. Source: Zambia Demographic and Health Survey 2013-2014

slight disruption to the process can negatively result into growth failure in terms of motor, cognitive and behavioural development. Also, early intervention in Zambia is yet to be established.

Ideally, all children are expected to pass through a typical pattern of development which is predictable. From 0 to 3 years, children record early developmental gains such as gross motor abilities (for example, sitting, crawling, standing and walking), expressive language abilities (such as cooing, babbling and short sentences to express desires), oral language processing and verbal memory [14]. No complex cognitive processes are expected at this point in time.

The emotional regulation as well as development and refinement of fine motor skills, sets a stage for child development between the third (3<sup>rd</sup>) and seventh (7<sup>th</sup>) years of life. Other landmarks during this period include visual memory, and ability to process given information quickly and accurately. The period that follows, (7 – 30 years) witnesses the development of high level cognitive abilities such as organizational skills, ability to process complex visual and auditory information and capacity to store and retrieve complex information [14].

All the cognitive processes involved between 0 to 3 years, take place alongside the development of brain structures, especially those associated with language and gross motor abilities [15]. During this period, there is a complex buildup of connecting structures in the frontal cortex of the basal ganglia of the brain [16]. Beside this, there is an expansion of a network of micro-vessels throughout the brain to support the on-going development [17].

Jean Piaget an eminent Swiss Psychologist has contributed immensely to our understanding of the cognitive development process of children right from infancy to the teenage years and beyond [18,19].

Piaget posited that there are four universal stages that humanity passes through in terms of cognitive development namely: Sensorimotor stage (Birth-2 years), Preoperational stage (2-7 years), Concrete Operational stage (7-11 years) and the Formal Operational stage (11 years-Adulthood).

According to Piaget in the Sensorimotor stage lasting from birth to about 2 years infants perceive the world primarily through their sensory abilities and through motor coordination. The infant initially is only capable of innate reflexes such as crying and grasping to the formation of the concept of object permanence at about 8 months (a realization that objects continue to exist even when out of sight of the infant's vision) to the rudimentary development of language in the last stages of the sensorimotor period [19].

In the Preoperational stage which lasts from about 2 years to approximately 7 years there is rapid refinement of language skills enabling children to represent the world symbolically through words and mental imagery as well as labeling objects they come into contact with. They are also capable of understanding the past (yesterday), the present (today) and the future (tomorrow). Children in this stage are egocentric meaning that they only perceive and interpret the world from their own perspective. Whatever they 'know' according to them is known by everyone. They are incapable of seeing the world from another person's perspective.

Children in the Concrete Operational stage lasting from about 7 years to about 11 years are now capable of mental operations although they still depend on the presence of tangible objects or actual events rather than theoretical conceptualization. The children in this stage are capable of understanding the concept of reversibility that actions can be reversed and the concept of decentration of thought where

they are capable of focusing on multiple dimensions of a problem simultaneously. The children in this stage get rid of their egocentricity and become aware of different possibilities of interpreting a situation rather than just from their own perspective.

In the Formal Operational stage which is the final stage of cognitive growth according to Piaget and which starts at about 11 years and goes into adulthood, the children are now capable of abstract thought and their mental operations are not tied to tangible objects or practical events. The many adolescents in this stage even enjoy questioning established theoretical norms and concepts in society such as morality and justice. They can go beyond the given just like many adults can especially in western societies. The problem solving abilities of Formal Operational children are now based on systematic logic objectively looking at solutions from a multidimensional approach rather than a one dimensional approach.

Piaget has contributed immensely to the understanding of children's cognitive development but his assumptions on the universality of the stages of cognitive development are increasingly under question. It is now acknowledged that culture has a big role to play in children's cognitive development and that some cultures especially nonwestern cultures do not emphasize the hierarchical reasoning activities which demonstrate the occurrence of cognitive development in children [19].

Passer and Smith [18] posit that whereas Piaget primarily focused on the child's own interaction with a given situation Vygotsky a Russian Psychologist emphasized the child's interaction with his/her social environment. Vygotsky's argument was that the cognitive development of the child occurred in a social world where the child interacted with the caregivers and therefore depended on them for his/her cognitive development to occur. Clearly children profit by learning from experienced people in their environment.

**The effect of HIV on growth and development in infants:** HIV has been linked to a wide range of developmental challenges such as cognitive failure, neurological symptoms, learning difficulties and speech and language problems [20]. Though it is difficult to isolate its singular effect on the neurological status of children infected with it, research has established that 90% of the HIV positive children have neurological problems [21].

As measured by the Bayley Scales of Infant Development, the cognitive and motor development of HIV positive children are usually delayed [22]. Nevertheless, developmental delay does not always involve both cognitive and motor development; some kids may only suffer from one and not the other. Similarly, the age of the onset also varies; with some beginning to experience these challenges from as early as three (3) months to as late as two (2) years [23].

Among the manifestations of HIV in infected children is impaired growth and development. Research evidence has shown that HIV positive children are usually characterized by abnormalities in growth, thereby putting their lives at high risk for morbidities. Not only is impaired development associated with childhood morbidity, but is also an indicator of disease progression, hence is a mortality risk factor [24]. Using neuropsychological tests to assess executive function problems in HIV positive children, memory and visual spatial abilities, Bisiacchi found that executive function scores were lower in HIV infected than HIV uninfected samples [25].

The negative effect of HIV on the physical development of the infected children has been documented, both in the developed and underdeveloped countries. Increased height and weight impairment

is observed as the child's age increases. As early as four (4) months of age, children begin to show symptoms of stunted growth before they eventually begin to lose their previous developmental gains [26]. Moye et al. observed in their study that compared to uninfected children, HIV infected children were lighter in weight and shorter than their counterparts [26].

Growth retardation has also been reported in Sub-Saharan African children with HIV. A study by Bailey et al., found a high prevalence of wasting (disproportionate body weight and height) after the first year of birth. Another comparative study conducted in Europe showed an average weight and height deficits of 7 kg and 7.5 cm by age 10 among HIV infected children compared to the uninfected group [27].

The physical development of a child begins in the womb. As such, in utero exposure to the HIV virus can severely impair the fetus' development even before its birth. Findings from studies conducted in Africa have indicated that the maternal HIV status can affect her pregnancy outcomes, both in terms of preterm delivery and low child birth weight [28-31]. However, this finding has not been reported in the developed countries, probably due to the presence of many maternal confounding factors such as drug use [32,33].

Whether or not maternal HIV status is an independent variable in pregnancy outcomes is not an argument at hand. The fact remains that many studies have shown that mean birth weights of children born to HIV positive mothers are generally lower than those born to HIV negative mothers. One study reported that the effect of in utero HIV infection on weight and length at birth was < 0.28 kg and < 1.64 cm compared to the HIV negative control group [24].

As regards neurocognitive development, "infants who acquired HIV during fetal and early life demonstrated poorer mean developmental scores than HIV-unexposed children. Mean motor and cognitive scores were consistently 1 to 2 SDs below the population mean. Mean scores improved if the infant received treatment before 12 weeks and or a more complex antiretroviral regime [34]. This has implications on the role of protease inhibitors or newer antiretroviral drugs and early intervention to improve outcomes for the young infant.

HIV has been associated with neuro developmental cognitive delays. Research has shown that once acquired, HIV invades the Central Nervous System (CNS) and replicates itself within it almost immediately [35,36]. Studies conducted on aborted fetuses of HIV mothers reveal the presence of HIV in the CNS as early as 15 weeks of pregnancy [37]. This tendency of HIV to invade the CNS is the common cause of delayed cognitive functioning in children, which results in HIV encephalopathy [38,39]. Encephalopathy is the most fatal and severe form of CNS complication, characterized by impaired brain growth and inability to achieve or retain previously acquired developmental milestones [40].

HIV-related encephalopathy comes in two forms: progressive and static [41]. Belman further subdivides progressive encephalopathy in two: plateau and sub-acute. Plateau progressive encephalopathy is a less severe form; characterized by a failure to make new neurocognitive and developmental milestones while retaining the already acquired abilities [41]. This is in sharp contrast to sub-acute progressive encephalopathy, which is more severe- involving a loss of previously gained developmental milestones as well as failure to acquire new ones [40]. Affected children generally lose social and cognitive functioning as evidenced by loss of speech, staring and lack of interest [41].

Static encephalopathy in children manifests through their non-

progressive abnormality in making developmental gains despite the fact that they continue to make gains [40]. In other words, HIV positive children present with impairments such as expressive language problems, attention, perceptual motor abilities and motor function deficits [38]. While, in the advent of ARVs, the prevalence of encephalopathy is believed to have reduced [42], it may not be the case in Zambia, where more than 50% of child deliveries are still being done in homes- away from health care facilities [42].

**Measuring normal and abnormal development:** With a long history of intervention, developmental paediatrics has accumulated a number of tools to measure the four areas of development, gross motor, fine motor and vision, speech and hearing and social, emotional and behavioural. There may be normal variations in the pattern of development.

Gross motor development progresses rapidly within the first two years from a supine bed bound newborn to an upright active toddler. The stages begin with head and neck control, to sitting, crawling, walking and then running. Fine motor skills begin with visual attention, pincer grip, then feeding, dressing and holding a pencil.

Speech and hearing is incremental from the startle of the newborn, cooing, single words, phrases then conversation. Socializing begins with the social smile at 6 weeks with friendly responsiveness up to 8 months after which separation anxiety, fear of strangers set in. The all important toilet training and self feeding happens during year two.

**Paediatric neuro behaviour and HIV:** The effects of HIV on the CNS can either be limited to (i) time or (ii) specific function as a result of the effects of the function that has been affected. The other effect may cause a developmental delay of a given area [43,44]. Research has indicated that a good number of children who are HIV positive exhibit neurological and developmental delays. Some of the characteristics of children who are HIV+ include decreased intellectual levels, mental retardation, specific learning difficulties, visual-spatial deficits, psychomotor impairments and decreased alertness. Communication and behavioural problems have been reported for children with HIV infection [45-48].

We present some studies that have been undertaken to explore the possible effects of HIV on the Central Nervous System.

**Effect of HIV on the central nervous system:** HIV infection is associated with various neurocognitive complications. These can range from subtle disorders in attention and memory to disabling dementia. Knight et al. [47] studied the mental and psychomotor development of 20 HIV+ and 25 seroreverted infants (ages 3-30 months) children with the Bayley Scales for Infant Development [22] at two intervals. They found that HIV+ infants had a significantly lower score on a test of motor development at baseline and follow-up compared to seroreverted infants. They further found that HIV+ children scored significantly lower than HIV negative children on a neurological test using the Psychomotor Development Index. In another related study, Nozyce et al. [45] characterized the behavioural and cognitive profiles of 274 clinically and immunologically stable antiretroviral-experienced HIV infected children. They correlated neuropsychological measures with age, and CD4 lymphocyte count. Their findings revealed that the children who were clinically and immunologically stable exhibited more frequent behavioural problems and lower developmental and cognitive scores than the established norms. They note that these children exhibited more psychosomatic, learning, hyperactivity, impulsive-hyperactive, conduct and anxiety problems.

Nichols et al. [48] investigated the changes that take place in children and adolescents who are HIV+. The participants were 277 HIV seropositive and 126 HIV-seronegative boys with hemophilia. They divided the participants into three groups based on trajectory of immune functioning. They report that the participants showed some resilience in adaptive behaviour, emotional and behavioural problems. This performance, however, diminishes over time. These studies are indicative of the effects that a depressed CD4 count may have on the cognitive functions of HIV positive children. Though some extension in life can be accounted for by HAART, the adaptive behavioural and emotional problems soon appear as a result of the diminishing CD4 count.

**Effect of antiretroviral treatment:** The preceding discussion has shown that deleterious effects of HIV on the CNS are varied. Studies on Highly Active Antiretroviral Therapy (HAART) regimens have had mixed reports. Here we highlight some of the effects of HAART on the neurocognitive functioning of HIV+ individuals. HAART is a combination of several antiretroviral drugs. This “cocktail” works to suppress the growth of the virus in the body of the infected individual.

Lindsey et al. [49] conducted a study to examine the effects of HIV infection and the impact of HAART with protease inhibitors on neurodevelopmental function during the first 3 years of life. Using the Bayley Scales of Infant Development, they measured the participants’ neurodevelopmental function. The children were tested before and after the introduction of HAART. They concluded that while HAART improved the children’s survival and immunological status, there was little improvement in the neurodevelopmental functioning in the young children.

In the study by Lindsey et al. [49], they focused only on children who had not been exposed to any form of education to see whether education would help improve their cognitive skills. Also the children were tested at an early stage and it is not clear to what extent HIV affects the child in the first few years of life. Age tends to play an important role in the way the HIV-virus affects the Central Nervous system. Hardy et al. [50] conducted a study on 257 adults with HIV-1. They administered a variety of neurocognitive tests to the participants. They conclude that age had an effect on the performance of the participants. The older participants who were HIV+ ( $M = 44.5$ ) performed worse than the younger HIV+ positive adults ( $M = 31.5$ ) on all measures.

In another study Shabthag et al. [40] assessed the impact of combination antiretroviral therapy on neurocognitive outcomes in perinatally HIV infected patients. They further examined whether CD4 percent and viral load were predictive of future neurocognitive function. They found that progressive encephalopathy decreased since the introduction of HAART. There was a weak association between viral load and neurocognitive scores ( $p = 0.06$ ) and CD4 percentage ( $p < 0.001$ ). They conclude that a combination of antiretroviral treatment is associated with neurocognitive improvements while viral load and CD4 percentage are marginally predictive of future neurocognitive changes.

Koekkoek et al. [51,52] has shown that there is a significant increase in the neuropsychological function of HIV+ children especially in their executive functions and the children have shown improvement in working memory and attention control after HAART. The results for psychomotor control have not been so encouraging. While there is a lot of optimism about the effects of HAART on life and the neurocognitive function of HIV+ individuals, the improvements are limited to a few areas only. Tozzi et al. [53] note that the HAART may not be as effective

as they used to be and so it may be necessary to consider alternative methods of reducing the effect of HIV on the CNS.

The literature has clearly shown that HIV affects the motor and cognitive development of HIV+ positive children negatively. It also can be stated that even though HAART may not completely reverse the effects of HIV on the physical and cognitive development of the children it is a welcome intervention which improves the lives of the recipient children in comparison to children not on HAART.

As other methods of intervention apart from HAART are sought it might be important to consider the socio cultural milieu of the children benefiting from the intervention. It is important that social cultural practices of the community are assessed so that the intervention rather than only being medical can also be educational especially aimed at changing the attitudes of the communities towards practices that might negatively affect the effect of the medical intervention.

Simple ‘practices’ such as knowledge on the nutritional status of the foods mothers can afford will make a difference as it is known that good nutrition on its own is very helpful in achieving positive medical results. As the fight to help children who are HIV+ continues education and knowledge transmission on non medical factors of the pandemic such as cultural and social practices will increasingly play a mediatory role in the improvement of the affected children’s lives.

## Conclusion

This paper reviews cognitive development in children and the effect of HIV on developmental and cognitive milestones from fetal life to adolescence. It captures events during the critical phase of development in the first 4 years, while noting essential phases in development that add up to the final outcome for the child with and without HIV. Issues identified include the importance of genetic makeup, presence of various infections including HIV, nutrition status, emotional deprivation, poverty, culture among others. The article sites a number of studies in children with HIV and its negative effects such as: subtle to overt neurobehavioral abnormalities, developmental delay, declining intellectual performance, specific learning difficulties, encephalopathy and dementia as a result of HIV in the brain.

The use of HAART was found to improve immunological status and survival over and above neurocognitive function. Older children tend to be worse off than younger children. HAART also improved neuropsychological function. However factors such as nutrition, social and cultural factors contribute to the overall positive life outcome for the child.

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