# NEUROCOGNITIVE FUNCTION IN HIV INFECTED CHILDREN: A SYSTEMATIC REVIEW OF LITERATURE

**Mr. Takudzwa. C. MARADZE**

*Department of Economics, Midlands State University, Harare, Zimbabwe*

**Dr. Smartson. P. NYONI**

*ZICHIRe Project, University of Zimbabwe, Harare, Zimbabwe*

**Mr. Thabani NYONI**

*Department of Economics, University of Zimbabwe, Harare, Zimbabwe*

**ABSTRACT**

*There is no doubt; HIV/AIDS remains one of the top epidemics leading to loss of lives at large scale. Neurocognitive impairments are evident in infants and adolescents and it is not yet clear whether it is HIV virus alone causing these. To date, studies that have been carried out show evidence that children with HIV have neurocognitive impairments, especially in developing countries, while their counterparts in the US and other developed nations have found better ways to exterminate these conditions, their cognitive functionality is improving and the life expectancy of HIV infected children has increased. However, these findings are not synthesized in a one-size-fit-all manner as the ways used to measure domains which determine cognitive ability differ. Also, domains looked at by various researchers differ from the child's intelligence, rearing environment, adherence to medication, type of guardian, child's memory and physical appearance of the children. It is the aim of this paper to use an ecological approach in conducting a systematic review that will identify the causes and effects of neurocognitive function in HIV infected children for both developed and developing countries. In addition, this systematic review will also assist policy-makers, communities and humanitarians to make informed and evidence-based decisions that help reduce the effects of neurocognitive function mainly in developing nations where HIV prevalence is still high.*

**Keywords: -** *Children, HIV, Neurocognitive Function*

## 1.0 INTRODUCTION

The World Health Organization (WHO, 2009) 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 went on to highlight that 86% of HIV-infected children in the world were from sub-Saharan Africa (SSA). 90% of these children are said to have acquired the infection from their mother during pregnancy (main mode of infection in young children), labor or delivery, or through breastfeeding (WHO, 2010). Evidence from the Jointed United Nations Programme on HIV/AIDS showed that HIV/AIDS claimed the lives of

380 000 in the year of 2006, had it been in 2009 it would have meant all of the newly infected children would have died. HIV infects the cells of the immune system by either destroying or impairing their function. If left unattended or not yet recognized, the infection develops within the body, the immune system turns out to be weaker and the child becomes more susceptible to infections. When HIV has fully advanced it will now be referred to acquired immunodeficiency syndrome (AIDS).

**1.1 Overview of the Condition**

Considerable evidence shows that, progress has been made in recent decades regarding the prevention of HIV infection. Despite these efforts, approximately 3.2 million children and adolescents around the world are living with perinatally acquired HIV (World Health Organization 2015b). Patel et al. (2008), pointed out that with treatment, these children will be more likely to survive into adulthood**.** Recent standard treatment classically consists of a combination of three medicines referred to as highly active antiretroviral therapy (HAART, World Health Organization 2015a). Off late research on the plausible effects of HAART to mitigate problems associated with neurocognitive development and performance is mixed in general and is particularly limited in children. Liner et al. (2010) and Whitehead et al. (2013) suggested that neurocognitive difficulties persist in the era of HAART medications and further research should be done to determine the extent of both the positive and negative effects and their conducive functioning environments.

It is, therefore, the aim of this paper to better understand the nature of the neurocognitive difficulties children with HIV may experience. According to Ellis et al. (2009), the central nervous system is damaged by HIV in two ways. The virus infects certain cells of the central nervous system (CNS) and produces various proteins that can damage neuronal cells and interfere with their functioning. In turn, the immune response to the virus by the cells may be impaired and inflammation may then persist (Wood et al.2009).

One more matter to take into account is that of the likely role of HAART medications in neurocognitive development of children. Some researchers found out that antiretroviral medications may be toxic to brain cells (Robertson et al.2012). As discussed by Liner et al. (2010), antiretrovirals can lead to mitochondrial dysfunction, destabilization of neuronal intracellular homeostasis, reduction of cell membrane potential, and dendritic beading and pruning. Thus, it may be that not only the disease but also the treatment may contribute to the progressive neurocognitive challenges seen in children with HIV. The eras before and after HAART finds compromised cognitive functioning in HIV infected children Lindsey (2007).

This suggests that in spite of better treatment that even reduced neurologic complications, HIV infection still penetrates the CNS. Lindsey et al. (2007, p. 687) argued that neurodevelopment is most probably induced by genetic, health, treatment, disease and psychosocial factors in the HAART time line. Other effects of HIV on infected children under the HAART era can be better classified under the ecological approach, which will be discussed later in this paper, issues like poverty violence and abuse, nutritional deficiencies, prematurity and prenatal drug abuse seen to affect cognitive development will be discussed.

A number of systematic reviews have been conducted to address developmental outcomes in children infected with HIV/AIDS, thus before and after the HAART era. However, these studies have found it difficult to carry out research that has generalized effects of HIV on

neurodevelopment due to diversity of measuring instruments and age of participants, this paper will try to amalgamate all effects under the ecological approach and determine their effects in HIV infected children.

### 1.2 Relevance of the Study

Sustainable Development Goal (SDG) 3 aspires to ensure health and well-being for all and a bold commitment to ending epidemics like AIDS by 2030, WHO (2015). It also aims to provide access to safe and effective medicines and vacancies for all. Focus of this goal is to also end preventable deaths for children below the age of 5 years, WHO (2015). One can see that the preservation and guarantee of quality of life becomes a more essential concern in the management of HIV. Faced with such a target better awareness of neurocognitive function of HIV is critical. This paper also notes that great strides have been made in HIV management and aims to identify the gaps that remain in eradicating cognitive and motor effects in HIV infected children. Already there is debatable evidence within available research on the effects of HIV on cognitive and motor development, however there are limitations imposed because of study designs, measuring instruments, study methodologies and study populations. Newell (2012) highlighted that not much focus was being put on the children over the past years, considering the effects HIV has on a developing infant and how these effects may differ from those of a fully grown adult who has had much of the attention. In order to plan for inclusive interventions, services, treatment and care it is of utmost important to comprehend the cognitive abilities and developmental milestones of HIV positive children. Considering the above, this paper seeks to systematically review the already available research and add more evidence on the effects and prevalence of neurocognitive function in HIV infected children in the world especially after the HAART era and come up with more inclusive interventions that do not leave out the HIV infected infant.

### 1.3 Objectives

The objective of this study is to conduct a systematic review on the prevalence and effects of neurocognitive function in HIV infected children in both developed and developing countries.

Other objectives:

i. To have a consolidation of literature that will help understand the effects and prevalence of neurocognitive function in HIV infected children and help design targeted and context-based interventions primarily for treatment of these vulnerable children.
ii. More so, this systematic review will also assist policymakers, stakeholders and humanitarians to make informed and evidence-based decisions and policies mainly in developing countries of Asia and Africa where the condition is more prevalent.

## 2.0 Methodology

The studies for this review were found by searching for articles published between 2009 and September 2020. Titles, abstracts, reference lists and full texts were assessed for inclusion and a search was conducted using combinations of the following terms: human immunodeficiency virus (HIV), acquired immunodeficiency virus (AIDS), prevalence, children, infants, adolescents, neurocognitive, neuro development and perinatal HIV. Article sources included PsycINFO, PsycARTICLES, Google Scholar, JSTOR and PubMed. Studies were included in this

review if they were in English, described original research and included a sample of at least five participants in which the majority of participants were less than 18 years old. Children had to have acquired HIV during the perinatal period.

### 2.1 Characteristics of Studies Selected for Review

Table 1: Studies selected for review

| First author, Year, Country | Study design | Title of Study | Neurocognitive Measures Used | Age Scale Used | Method Used to Test for HIV |
|---|---|---|---|---|---|
| **Kenechukwu K. IIoh, 2017, Nigeria** | Cross sectional | Neurocognitive Function of School-aged HIV infected Children in Enugu, Nigeria | Raven's progressive matrices (RPM) test | 6-15 years | -Viral markers -DNA polymerase chain reaction |
| **Kandawasvika GQ, 2011, Zimbabwe** | Cross sectional | Neurodevelopmental impairment among infants born to mothers infected with human immunodeficiency virus and uninfected mothers from three peri-urban primary care clinics in Harare, Zimbabwe | Bayley Infant Neurodevelopmental Screener (BINS) | From 6 weeks; 3,6,9,12 and 15 months post delivery | -DNA polymerase chain reaction -Rapid HIV antibody tests -Oraquick |
| **Ravindran O. S., 2014, India** | Cross sectional | Cognitive Deficits in HIV Infected Children | -Comprehensive neuropsychological battery. -Malin's Intelligence Scale | 8-9 years | -Oraquick -ART initiation register |
| **Theodore D. Ruel, 2012, Uganda** | Cross sectional | Neurocognitive and Motor Deficits in HIV-Infected Ugandan Children With High CD4 Cell Counts | -Test of Variables of Attention (TOVA) -Kaufman Assessment Battery for Children, second edition (KABC-2) | 6-12 years | -PCR tests |
| **Sophie Cohen, 2015, Netherlands** | Cross sectional | Poorer cognitive performance in perinatally HIV-infected children versus healthy | Multivariate normative comparison of cognitive domains | 2-17 years | -Oraquick -PCR tests |

| | | | | | |
|---|---|---|---|---|---|
| | | socioeconomically matched controls | | | |
| **Natasha A. Dobrova-Krol, 2010, Ukraine** | Cross sectional | Effects of Perinatal HIV Infection and Early Institutional Rearing on Physical and Cognitive Development of Children in Ukraine | Wechsler Preschool and Primary Scales of Intelligence-Revised<br>Kififi scale | Less than 5 years | Positive viral culture of polymerase chain reaction assay |
| **Smith R, 2012, USA** | Cross sectional | Impact of Human Immunodeficiency Virus Severity on Cognitive and Adaptive Functioning during Childhood and Adolescence | Wechsler Intelligence Scale for Children (WISC-IV)<br>Adaptive Behavior Assessment System (ABAS-II) | 7-16 years | -Viral markers<br>-ART initiation register |
| **Gillian D Furguson, 2009, South Africa** | Cross sectional | The prevalence of motor delay among HIV infected children living in Cape Town, South Africa | Bayley Scales of Infant Development | 6 weeks to 5 years | -Viral markers<br>-ART initiation register |
| **Kathleen M. Malee, 2011, USA** | Cross sectional | Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure | Behavior Assessment System for Children-Second Edition, (BASC-2 | 7 to 16 years | biological markers |
| **Koekkoek, S, 2008, Netherlands** | Cross sectional | Neurocognitive function profile in HIV-infected school-age children. | Global intelligence test and tests from the Amsterdam Neuropsychological Tasks (ANT) program. | 5 to 12 years | Biological markers |

**Source**: Reviewed Literature (2020)

### 2.2 Neurocognitive Function in HIV Infected Children

Table 2: Summary - Neurocognitive Function in HIV Infected Children

| Author(s) | Year | Neurocognitive function and HIV infected children | Secondary Findings |
|---|---|---|---|
| **Kenechukwu K. IIoh et al** | 2017 | -Poor cognitive functioning among school-aged HIV- | -HIV infected children with a low socioeconomic status had |

| | | | |
|---|---|---|---|
| | | positive children was seen to be explained by the direct effects of HIV on neurodevelopment during the first few years of life<br>-HIV also had an indirect effect on neurodevelopment through recurrent opportunistic Infections it paved way for(immunosuppression). | below-average intelligence and lived in less stimulating and supportive home environments.<br>-Lower maternal educational attainment worsened cognitive functions |
| **Kandawasvika GQ et al** | 2011 | -Higher risk<br>for neurocognitive function was observed early among the infants infected with<br>HIV by 3 months of age.<br>-CNS disease on the developing brain was observed in infected children as early as 3 months old. | -Low socioeconomic<br>status, presence of a sick caregiver, nutritional factors and lack of infant stimulating home environment<br>influenced neurodevelopment even<br>in the uninfected children.<br>-Reduced head circumference for age has been associated<br>with developmental delay. |
| **Ravindran, O. S. et al** | 2014 | -HIV‑infected children experience difficulties with their daily living and social functioning when compared with<br>peers of the same age without a chronic illness.<br>-Neurocognitive conditions did not improve even after ART initiation, undetectable viral load and normal<br>CD4 cell. | -Family structure and child rearing played a vital<br>role in the neurodevelopment of the infected child.<br>-Poverty and<br>low socioeconomic status was linked to poor<br>neurocognitive development |
| **Theodore D. Ruel et al** | 2012 | -ART must be initiated soon after infection and before CD4 cell counts decrease to prevent irreversible impairment at critical stages in<br>neurodevelopment. | |
| **Sophie Cohen et al** | 2015 | -Cognitive performance of HIV-infected children was poor | |
| **Natasha A. Dobrova-Krol** | 2010 | -Both HIV infection and institutional care were related | -Family care, even of compromised quality, was |

| | | | |
|---|---|---|---|
| **et al** | | to delays in physical and cognitive development, with a larger effect of the rearing environment | found to be more favorable for children's physical and cognitive development than institutional care |
| **Smith R et al** | 2012 | -Early preventive therapy may be critical in reducing risk of later neurodevelopmental impairments.<br>-Adaptive functioning proved that youth have adequate skills to manage the demands of everyday life, regardless of past severe illness or cognitive functioning | -Better cognitive outcome was connected with having a biological parent as caregiver and higher family income level.<br>-Other poorer cognitive outcomes included being non-white, having an indigenous language other than English. |
| **Gillian D Furguson et al** | 2009 | -HIV infected children who had more hospital admissions, single, unemployed and uneducated caregivers, were seen to have poorer performance<br>- | . |
| **Kathleen M. Malee** | 2011 | -HIV infected children and perinatal HIV exposed adolescents were seen to have high odds of having a mental illness and poor psychological adaptation throughout childhood | -Psychiatric disorders, like depression, disproportionately affected women with HIV/AIDS, thus increased risk for negative outcomes. |
| **Koekkoek, S et al** | 2008 | -HIV-infected children performed poorer on several neuropsychological tests<br>-Higher CD4% at initiation of highly active antiretroviral therapy (HAART) and longer treatment duration were associated with better working memory function and attentional control | |

**Source**: Reviewed Literature (2020)

## 3.0 PREVELENCE AND EFFECTS OF NEUROCOGNITIVE FUNCTION IN HIV INFECTED CHILDREN: A BRIEF DISCUSSION

This systematic review evaluated the current growing scientific evidence on cognitive impairment in perinatally HIV-infected children and adolescents. Emphasis was on trying to help inform clinical practice guide the development of future interventions to improve the cognitive

well-being of this vital populace throughout its life trajectory. In contrast this review captures the shift of studies from the USA to sub-Saharan Africa, the deeper understanding of cognitive challenges and the complexity of effects. L. Sherr et al. (2014), in their review noted that 60% of studies were from the USA in 2009 and this has reduced to 43% reflecting the reality that the majority of HIV positive children live in Sub-Saharan Africa and the attention which is now being focused on this group, this has also been the case in this review as the majority of studies reviewed were from developing countries.

The studies acknowledged in the review showed more complex design including a greater array of measures with a wider coverage of cognitive domains. These serve to initiate understanding into a more complex understanding of cognitive performance, development and behavioral concepts usually included under the broad scope of cognitive function. The broad areas of challenge for children with HIV infection are becoming clear with time. Experience from these settings suggests that HIV is a major determinant of neurocognitive dysfunction, this has been agreed upon by most of the researchers reviewed. The main question was which environments promote the prevalence and effects of HIV in infected children and how neurocognitive function comes about. Lack of a consistent research protocol is likely contributing to the mixed results obtained in previous research and the difficulty with the etiology of the neurological issues observed in children with HIV (Hoare et al. 2014). It may also make it difficult to compare studies completed in industrialized countries to those completed in developing countries and vice versa.

Kayla A. Musielak (2016) recommended the use of an ecological approach to conceptualize the challenges facing children and families with HIV and to use this framework for selecting variables for inclusion in research related to children with HIV. Doing so provided a consistent framework for future research that takes into account the broad interactions of variables contributing to developmental outcomes for children with HIV. It also would allow for sufficient information to be collected and disseminated so that accurate population-based comparisons can be made between studies.

## 4.0 AN ECOLOGICAL APPROACH IN UNDERSTANDING NEUROCOGNITIVE FUNCTION

Ecological systems theory of Bronfenbrenner (1979) describes that there are four levels of environments that are involved in the development of a person: the *microsystem, mesosystem, exosystem,* and *macrosystem*. The *microsystem* is the immediate environment around the person, including the home, neighborhood, school, religious, and other settings, and the individuals within those places for example the guardians, care givers and teachers. As for the *mesosystem,* it includes the interactions between microsystem settings. For example, children who experience trauma in the home may be oppositional in the classroom setup. *Exosystem* refers to situations that the person is not actively involved in, but that influences the development of the person. Examples of exosystem settings include community resources and mass media. Finally, the *macrosystem* is the cultural setting in which the person develops and includes the belief systems, norms, and policies that affect the individual.

### 4.1 The Microsystem of an HIV Infected Child and Neurocognitive Function

Children with HIV experience have many individual factors related to HIV that need to be taken into account. These include immune system status, viral load and clinical stage, all relate to the

virus itself. Other individual factors which may be unrelated to HIV that influence neurocognitive development and need to be assessed include exposure to substances and secondary infections in utero, prematurity and birth weight, and early experiences of trauma because these are all variables known to influence brain development (BirkIrner, 2012; Hack et al., 2000) More microsystem factors may include educational experiences and caregiving issues for example orphan hood and quality of caregiving. Previous research indicates that these are important issues for children affected by HIV. Some environmental factors affecting cognitive and motor development where children live include: poverty, violence and abuse, and prenatal drug abuse Kullgren et al (2004). 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.

Ravindran et al (2014), found that HIV infection may have a direct effect on neurodevelopment during the first few years of life, which is the time of rapid brain development occurs. He went on to highlight that HIV may have an indirect effect through recurrent/opportunistic infections that may lead to poorer general health of an infant. A Tanzanian study on HIV-infected infants reported that infants with utero infection had higher risk of delayed mental functioning compared to infants who were diagnosed at a later stage of life[1] Cohen et al (2015) also found out that HIV-positive children performed more poorly than controls in all cognitive domains, but most notably on attention, general intellectual functioning, processing speed and working memory.

Prematurity is also correlated with developmental delay, and it is well documented that HIV infection during pregnancy may elevate premature delivery rates (Townsend et al., 2010). Ruel et al (2012) advocated that neurocognitive deficits in HIV-infected African children did not only relate to the pathophysiology of HIV infection but also to poor nutrition and alterations in the home environment that result from HIV illness among providers and caregivers. Ruel et al (2012), also found out that Malaria can also lead to neurocognitive impairment, these results were similar to those got by Boivin et al (2007) were parasite-filled blood cells blocked small blood vessels in children's brains (cerebral malaria). Dobrova-Krol et al (2010) cautioned that the presence of institutionalized rearing was associated with negative outcomes more so than HIV status. The environment within which the children are raised seems to be an important factor in the course of their developmental outcome. neurocognitive delay risks were seen to be compounded in infected children especially when exposed to the virus, parental death and were in institutionalized care.

Ferguson and Jelsma (2009) noted that in addition to different outcome scores, children with HIV also had single parents, significantly more hospital admissions, and differences in housing environments. These overriding variables may contribute to cognitive development via environmental stimulation and learning opportunity. The two also found out that parenting and stimulation also appeared to be a factor to consider in child cognitive development, as infected children in foster care also performed poorly. Ravindran et al (2014), highlighted that family structure and child rearing had a pivotal role in the neurodevelopment of the child. In his study all the HIV‐infected children who were under the care of home authorities due to poverty in their families, hence they performed poorly when compared to children who lived with their parents. This finding is similar to a U. S. study by Maleea et al. (2011), which reported that children living with their biological parents were less likely to manifest conduct or learning problems when compared to those living with others. Maleea et al. (2011) noted that children with HIV

had more problems in comparison to exposed but uninfected children, she went on to highlight that caregiver characteristics were associated with higher odds of problems like psychiatric disorder and health related functional limitations. Caregivers with psychiatric disorders were often seen to be in misery and were a psychological risk among their children. Psychiatric disorders, such as depression, disproportionately affected women with HIV/AIDS. As a result, HIV-exposed children, whether HIV-infected or uninfected had increased risk of negative outcomes, such as emotional and behavioral problems, poor school and social adaptation, specific risk for depression and elevated rates of internalizing behaviors.

### 4.2 The Mesosystem of an HIV Infected Child and Neurocognitive Function

The mesosystem looks at the interaction of variables within the domains of the microsystem. Caregivers of children with HIV may experience difficulties with maintaining employment and accessing adequate health care and nutrition, Maleea et al. (2011). This will greatly affect the children and they will develop poorly. The socio-demographic and nutritional profile of the children are also analyzed under the mesosystem, with maternal education, poor household intellectual stimulation and malnutrition negatively impacting on neurocognitive development. Kandawasvika et al (2011), observed that nutritional deficiencies such as the lack of vitamin A, iodine, iron, inadequate caloric and protein intake affected both physical and cognitive development A number of systematic reviews have been conducted to address developmental outcomes in children infected with HIV/AIDS. Hoare et al. 2014 and Sherr et al. 2014) agreed on the fact that a range of family, resource and health-related influenced the neurocognitive development of children.

### 4.3 The Exosystem of an HIV Infected Child and Neurocognitive Function

The exosystem highlight the need for the inclusion of variables related to socioeconomic status of the family. Other factors that may affect the development of a child with HIV include, marital status, maternal HIV status, infant sex, or use of prophylactic ART. The wide range of economic and social environments for children may need to be controlled more carefully given their independent contributions on child outcome. IIoh et al (2017) found out that children from lower socioeconomic class were about three times more likely to have below-average intelligence. This is so as children from families of low socioeconomic status are more likely to live in less stimulating and supportive home environments. Kandawasvika GQ et al (2011), also observed that unfavorable home environmental factors such as an unstable caregiver, maternal alcohol abuse, and low level of maternal education put children at risk for developmental dysfunction. In the African context, the role of the extended family in infant neurodevelopmental outcome needs to be further explored as most household live from hand to mouth and having an HIV infected child would only mean an extra burden.

### 4.4 The Macrosystem of an HIV Infected Child and Neurocognitive Function

In understanding the macrosystem, one has to note that countries and international organizations create policies related specifically to the management of HIV, for example WHO guidelines for ART and HAART. These guidelines are macrosystem issues and they relate to the development of children with HIV, hence the need to assess children's ART initiation, ART duration, ART regimens, and ART adherence. Another important macrosystem issue affecting populations with HIV may be the stigma toward HIV embedded within a culture, which affects mental health status and medication adherence especially in the African context where HIV maybe seen to be

associated with the evil spirits and bad luck. As part of the recent changes to HIV treatment guidelines, it is probable that the presence of ART during infancy and early childhood, may influence the effect of the virus on the child's rapidly developing CNS and have an effect on how the child's immune system responses to the virus. Moreover, the newer medication guidelines help elongate the exposure to possibly neurotoxic medications. Overall, these factors may result in neurological effects which will be different from those of children who were exposed to dissimilar medications and who were treated for less time in accordance with earlier ART guidelines. In this systematic review antiretroviral treatment was considered in terms of its effects and relationship to cognitive performance. Koekkoek et al., (2008) pointed out that CD4 count at initiation of treatment was a predictor of cognitive performance, this is the same for the duration of treatment.

More than 2.3 million children younger than 15 years old are living with HIV, of which 90% are living in Africa (WHO pediatric advocacy toolkit, 2011). Every day almost 800 HIV positive children, without access to HIV care and treatment die. Only 28% of children who require treatment are receiving it compared to 37% of adults. In some African countries the differences between children and adults on treatment is greater (WHO pediatric advocacy toolkit, 2011). In terms of cognitive performance, antiretroviral treatment may work in two ways. Initially, the treatment will possibly stop future infections therefore ensuring less hospitalization for HIV positive children and they will have increased availability/attendance at schools. The next possible way is that the treatment may diminish viral load directly. In adult literature choice of compounds seems to be important given differential rates of brain barrier permeation, but yet to be examined in children Koopmans et al (2009). Evidence on the effects of antiretroviral is varied. Jelsma et al. (2011) reported that antiretroviral treatment did not always result in restoration of cognitive performance. Lowick et al. (2012) noted a fold increase in severe delay in HIV infected children compared to control children. Colombo GL et al., (2013) highlighted that being on combination antiretroviral therapy for a year was associated with modest improvements in neurocognition, thus attention, processing speed and executive performance improved. Information on initiation and duration of treatment in necessary, as well as more detail on the type of régime and those containing protease inhibitors needs to be known.

## 5.0 RECOMMENDATIONS

In 2009, an estimated 1.4 million HIV exposed infants were born but only 6% received early infant diagnosis services and were initiated on ART (WHO, 2011). Some infants who are tested may not receive their results and only a third who test positive initiate ART (WHO pediatric advocacy toolkit, 2011) Policy for these children is urgently required. This paper recommends that adequate and appropriate HIV management is rolled out in the following ways:

i. HIV tests must continue to be prompt and regular as they establish the HIV status of each child. Adoption of the use of Rapid tests and Oraquick is advised.
ii. Treatment rollout to all infected children should continue consistently. Information on the neuro-properties of treatment on children should be made known to guardians, this may be done by home visits or distribution of information pamphlets.
iii. On a macro level, guidelines on HIV need to include specific instructions on children. It is advised that there should be a shift in national treatment guidelines, they should ensure early introduction of HAART, and be committed to early intervention in child development programmes that lead to reduced prevalence of CNS deficits and improved

neurocognitive outcomes. These may be monitored and enforced by Humanitarian organizations like UNAIDS and they create country specific /customized guidelines for each nation not to remain behind.

iv. According to SDG 4, children have the right to education and this study clearly indicates the need for more special education provision for HIV positive children. Syllabuses must be tailored to meet these children's needs and current capabilities. If educated HIV infected adolescents will have their decision-making skills enhanced to better manage and reduce risks associated with life and the virus. Examples where this virus knowledge will apply is when disclosing one's status, negotiating for safe sex, dealing with stigma and understanding behavioral change.

v. Cognitive development, overall, is a neglected area of study and provision. Baseline and repeated measures are not routinely collected and repeated for children, we recommend nations to make special attention to these. Clinic staff should be trained and sent to workshops that equip them with skills to respond to a child with cognitive deficits. The area has moved forward for adults, but assessment and treatment for children lags behind.

vi. It is recommended that the developmental performance of HIV infected children be monitored over an extended period to determine whether the developmental delay can be reduced with treatment. In the interim, there is a need to provide stimulation and treatment to the large number of children who are developmentally delayed as a result of HIV infection, including those uninfected children in the community who are at risk owing to their socio-economic status. A Monitoring, Evaluation and Learning (MEAL) approach should be adopted with measurable outcomes at every interval.

vii. Integration of an early infant neurodevelopmental screening programme into child HIV management protocols will assist in the early referral of HIV-exposed children, these can be implemented from grassroot levels going up.

viii. Counselling pregnant mothers who participate in PMTCT services should emphasize the importance of early infant diagnosis so that necessary treatment, growth, and neurodevelopmental monitoring is initiated early to mitigate the detrimental effects of HIV infection.

ix. Multi-level, family-focused and evidence-based psychological and psychiatric intervention services that begin early in life should be adopted as they address both youth and caregiver competencies and needs. This may be the most efficacious and cost-effective way to deal with mesosystem domains

x. Collaboration with educators and schools at community level is also essential so that children receive the educational and social support that foster development of competency and adaptation in the school and home environments. In Africa specifically matters to deal with marginalization of those infected with HIV should be dealt with and village heads and field workers must be equipped with skills to better collaborate HIV positive communities and provide support

## 6.0 CONCLUSION

HIV infected children are, indeed, vulnerable to major neurocognitive deficits and they are likely to perform badly when it comes to their intelligence, memory and adaptability domains. From the reviewed literature we found that HIV alone may not lead to all the neurocognitive conditions being experienced by infected children. We found that HIV was complemented by other factors, the socalled, ecological features. These included factors like, ART guidelines caregiver poor emotional state, resource poor settings, lower socioeconomic status and poor

nutrition which all lead to the high prevalence of cognitive impairments and their effects. It is the hope of this paper that strategies aimed at poverty alleviation and good nutritional management are sort and they help complement early infant diagnosis and treatment of HIV in order to prevent neurocognitive impairment.

**REFERENCES**


1) Birk Irner, T. (2012). Substance exposure in utero and developmental consequences in adolescence: a systematic review. *Child Neuropsychology,* 18(6), 521–549. doi:10.1080/09297049.2011. 628309.
2) Boivin MJ, Bangirana P, Byarugaba J, et al. Cognitive impairment after cerebral malaria in children: a prospective study. *Pediatrics* 2007; 119:e360–6.
3) Bronfenbrenner, U. (1979). The ecology of human development: experiments by nature and design. *Cambridge: Harvard University Press*.
4) Chase, C., Ware, J., Hittelman, J., Blasini, I., Smith, R., Llorente, A., et al. (2000). Early cognitive and motor development among infants born to women infected with Human Immunodeficiency Virus. Women and infant's transmission study group. *Pediatrics,* 106(2), e25.
5) Cohen S, Ter Stege JA, Geurtsen GJ, et al. Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. *Clin Infect* Dis.2015;60(7):1111–1119
6) Colombo GL, Di Matteo S, Antinori A, Medaglia M, Murachelli S, Rizzardini G. Economic evaluation of initial antiretroviral therapy for HIV-infected patients: an update of Italian guidelines. *Clinicoecon Outcomes Res*. 2013; 5:489-496 https://doi.org/10.2147/CEOR.S48246
7) Dobrova-Krol, N. A., Bakermans-Kranenburg, M. J., Van IJzendoorn, M. H., & Juffer, F.(2010). The importance of quality of care: Effects of perinatal HIV infection and early institutional rearing on preschoolers' attachment and indiscriminate friendliness. *Journal of Child Psychology and Psychiatry*, 51(12), 1368–1376.
8) Ellis, R. J., Calero, P., & Stockin, M. D. (2009). HIV infection and the central nervous system. *Neuropsychological Review*, 19, 144–151. doi:10.1007/s11065-009-9094-1.
9) Ferguson, G., & Jelsma, J. (2009). The prevalence of motor delay among HIV infected children living in Cape Town, South Africa. *International Journal of Rehabilitation Research*, 32(2), 108–114.
10) McGrath N, Fawzi WW, Bellinger D, Robins J, Msamanga GI, Manji K, et al. The timing of mother‐to‐child transmission of human immunodeficiency virus infection and the neurodevelopment of children in Tanzania. *Pediatr Infect Dis J* 2006; 25:47‐52.
11) Hack, M., Wilson-Costello, D., Friedman, H., Taylor, G., Schluchter, M.,& Fanaroff, A. A. (2000). Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g. *Archives of Pediatrics and Adolescent Medicine,* 154(7), 725–731. doi:10.1001/archpedi.154.7.725.
12) Hoare J, Fouche J, Spottiswoode B, et al. Diffusion tensor imaging and neurocognotive study of HIV-

positive children who are HAART-naive 'slow progressors'. *J Neurovirol* 2012;18:205–12.

13) Hoare, J., Ransford, G. L., Phillips, N., Amos, T., Donald, K., & Stein, D.J. (2014). Systematic review of neuroimaging studies in vertically transmitted HIV positive children and adolescents. Metabolic Brain Disease, 29, 221–229. doi:10.1007/s11011-013-9456-5.

14) Iloh KK, Emodi IJ, Ibeziako NS, Ikefuna AN, Ubesie AC, Iloh ON, Ilechukwu GC, Ayuk AC. Neurocognitive Function of School-aged HIV-infected Children in Enugu, Nigeria. J Trop Pediatr. 2017 Dec 1;63(6):425-430. doi: 10.1093/tropej/fmx006. PMID: 28334859.

15) Kandawasvika GQ, Kuona P, Chandiwana P, et al. The burden and predictors of cognitive impairment among 6- to 8-year-old children infected and uninfected with HIV from Harare, Zimbabwe: a cross-sectional study. *Child Neuropsychol* 2015;21:106–20.

16) Koekkoek, S., De Sonneville, L. M., Wolfs, T. F., Licht, R., & Geelen, S. P. (2008). Neurocognitive function profile in HIV-infected school-age children. *European Journal of Paediatric Neurology*: EJPN: *Official Journal of the European Paediatric Neurology Society*, 12(4), 290.

17) Koopmans, P. P., Ellis, R., Best, B.M., & Letendre, S. (2009, Jun). Should antiretroviral therapy for HIV infection be tailored for intracerebral penetration? *Netherlands Journal of Medicine*, 67(6), 206–211.

18) Kullgren, K.A., Morris, M.K., Bachanas, P.J., & Jones, J.S. (2004) Prediction of Cognitive, Adaptive, and Behavioural Functioning in Preschool and School-Age Children with HIV. *Children's Health Care*, 33(4), 241-256.

19) Lindsey, J.C., Malee, K.M., Brouwers, P., & Hughes, M.D. (2007). Neurodevelopmental Functioning in HIV-Infected Infants and Young Children Before and After the Introduction of Protease Inhibitor Based Highly Active Antiretroviral Therapy. Pediatrics, 119(3), e681.

20) Liner, K. J., II, Ro, M. J., & Robertson, K. R. (2010). HIV, antiretroviral therapies, and the brain. Current HIV/AIDS Reports, 7, 85–91. doi:10.1007/s11904-010-0042-8.

21) Lowick, S., Sawry, S., & Meyers, T. (2012). Neurodevelopmental delay among HIV-infected preschool children receiving antiretroviral therapy and healthy preschool children in Soweto, South Africa. Psychology, Health & Medicine, 17(5), 599–610.

22) Maleea, K. M., Tassiopoulos, K., Huo, Y., Siberry, G., Williams, P. L., Hazra, R., et al. (2011). Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure. AIDS Care, 23(12), 1533–1544.

23) Musielak KA , Fine JG. (2016) An updated systematic review of neuroimaging studies of children and adolescents with perinatally acquired HIV. *J Pediatr NeuropsycholJune2016*; 2:34–49

24) Newell M, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P & Dabis F (2004) Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet 364, 1236–1243.

25) Patel, K., Hernan,M. A.,Williams, P. L., Seeger, J. E., McIntosh, K., van Dyke, R. B., & Seage, G. R., III. (2008). Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clinical Infectious Diseases*, 46, 507–515. doi:10.1086/526524.

26) Robertson, K., Liner, J., & Meeker, R. B. (2012). Antiretroviral neurotoxicity. *Journal of Neurovirology*, 18, 388–399. doi:10.1007/ s13365-012-0120-3.

27) Ruel TD, Boivin MJ, Boal HE, et al. (2012) Neurocognitive and motor deficit in HIV-infected Ugandan children with high CD4 cell counts. *Clin Infect Dis* ;54:1001–8.

28) Ravindran OS, Rani MP, Priya G .Cognitive deficits in HIV infected children. Indian J Psychol Med.2014;36(3):255–259

29) Smith R, Chernoff M, Williams PL, et al; (2012) Pediatric HIV/AIDS Cohort Study (PHACS) Team. Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *Pediatr Infect Dis J.* ;31(6):592–598

30) Sherr, L., Croome, N., Parra Castaneda, K., Bradshaw, K., & Herrero Romero, R. (2014). Developmental challenges in HIV infected children— an updated systematic review. *Children and Youth Services Review*, 45, 74–89. doi:10.1016/j .child youth.2014.03.040.

31) Townsend, C. L., Schulte, J., Thorne, C., Dominguez, K. L., Tookey, P. A., Cortina-Borja, M., et al. (2010). Antiretroviral therapy and preterm delivery—A pooled analysis of data from the United States and Europe. BJOG: *An International Journal of Obstetrics & Gynaecology*, 117(11), 1399–1410.

32) UNAIDS.AIDSEpide micUpdate:december2007.http://data.unaids.org/pub/epislides/2007/2007_epiupdate_en.p df (Accessed 23rdOctober 2020).

33) Whitehead, N., Potterton, J., & Coovadia, A. (2013). The neurodevelopment of HIV-infected infants on HAART compared to HIV-exposed but uninfected infants. AIDS Care: Psychological and Sociomedical Aspects of AIDS/HIV, 26(4), 497–504. doi:10. 1080/09540121.2013.841828.

34) WHO pediatric advocacy toolkit (2011). Available from. http://whqlibdoc.who.int/hq/ 2011/WHO_HIV_11.04_eng.pdf (Accessed 18th October 2020).

35) Wood, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychology Review*, *19*, 152–168. doi:10.1007/a11065-009- 9102-5.

36) World Health Organization (WHO). (2006). WHO case definition of HIV surveillance and revised clinical staging and immunological classification of HIV related disease in adults and children

37) World Health Organization. (2009). WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: WHO Press, World Health Organization.

38) World Health Organization. (2008). Report of the WHO Technical Reference Group. Paediatric HIV/ART Care Guideline Group meeting. Retrieved from http://www.who.int/hiv/pub/paediatric/WHO_ Paediatric_ART_guideline_rev_mreport_2008.pdf

39) World Health Organization. (2010). Antiretroviral therapy for HIV infection in infants and children: towards universal access. Retrieved from http://www.who.int/hiv/pub/paediatric/infants2010/en/

40) World Health Organization. (2013). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Retrieved from http://www.who.int/hiv/pub/guidelines/arv2013/ download/en/

41) World Health Organization. (2015a). Antiretroviral therapy. Retrieved from http://www.who.int/topics/antiretroviral_therapy/en/

42) World Health Organization. (2015b). Treatment of children living with HIV. Retrieved from http://www.who.int/hiv/topics/paediatric/hivpaediatric- infopage/en/