Scientific Research Publishing

International Journal of Clinical Medicine, 2018, 9, 495-504
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

HIV Encephalopathy (HIVE) in Children at the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria

Nsirimobu Ichendu Paul*, Boma Alali Ngozi Okoh, Edward Achinike Daniel Alikor

Department of Paediatrics and Child Health, University of Port Harcourt, Port Harcourt, Nigeria
Email: *nsirimobu.paul@yahoo.com

How to cite this paper: Paul, N.I., Okoh, B.A.N. and Alikor, E.A.D. (2018) HIV Encephalopathy (HIVE) in Children at the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria. *International Journal of Clinical Medicine*, **9**, 495-504.
https://doi.org/10.4236/ijcm.2018.96042

Received: April 14, 2018
Accepted: June 2, 2018
Published: June 5, 2018

Abstract

Background: HIV encephalopathy (HIVE) is associated with cognitive impairment in children with HIV infection, early diagnosis and initiation of HAART may reduce the morbidity associated with HIVE. **Objective**: To determine the prevalence of HIVE and associated comorbiditiesin children at the UPTH. **Methodology:** This was a retrospective study carried out from January to June 2017. The case notes of all HIV positive children presenting to the Paediatric Department of the University of Port Harcourt Teaching Hospital (UPTH) were studied. Children who met the diagnostic criteria for HIVE according to the Centre for Disease Control (CDC) definition were selected. The socio-demographic characteristics of the patients, mode of HIV transmission, CD4 count and associated comorbidities in these children were retrieved from the case notes. Obtained data was analyzed using Epi Info version 7.2. Comparisms of subgroups was carried out using the chi square test while statistical significance at 95% confidence interval was p value < 0.05. **Results:** A total of thirty five out of the 196 HIV positive children presenting to the hospital had HIV encephalopathy (HIVE) giving a prevalence rate of 17.9%. Of these 35 children, 18 were males and 17 females, giving a male to female ratio of 1:1. The mean age of the children was 5.7 ± 3.1 years. The mean age for the males was 6.4 ± 3.2 years and 5.0 ± 2.8 years for the females. There was no statistically significant difference observed between the sexes ($t = 1.35$, $p = 0.187$). Thirty (85.7%) of the patients with HIVE were on HAART at diagnosis. The mean age at diagnosis of HIV was 3.2 ± 3.1 years and the mean age at diagnosis of HIV encephalopathy was 3.4 ± 3.2 years. The documented route of transmission for all the subjects was mother-to-child-transmission (MTCT). Seventy five percent of the children were breastfed from birth and at 6 months all the mothers had discontinued breastfeeding. The mean CD4 count was 1053 ± 630 cells/ml. Tuberculosis

was the most prevalent co-morbidity occurring among the patients. **Conclusion:** The prevalence of HIVE in children at the UPTH is high and Tuberculosis is the commonest comorbidity. Early infant diagnosis, use of modern diagnostic tool and early initiation of HAART are advocated to reduce its associated morbidity.

Keywords

HIV, Encephalopathy, Children, UPTH

1. Introduction

Approximately 1.8 million children worldwide are living with Human immunodeficiency Virus (HIV) or Acquired immune deficiency syndrome (AIDS) with over 90% of them living in sub-Saharan Africa according to the World Health Organization (WHO) report 2015 [1] [2] [3]. In Nigeria, there is an estimated 340,000 HIV-infected children not yet receiving antiretroviral therapy (ART), with an estimated 48,000 new infections among children annually [2] [3]. These figures represent mainly vertically transmitted HIV, which includes infection in utero, peri-partum and from breast milk [2] [4] [5].

Neurological manifestations of HIV infection occur in both children and adults. HIV Encephalopathy (HIVE), the most common primary HIV-related Central Nervous System (CNS) complication, is believed to be due to the damaging effects of the virus on the immature fetal and infant brain following early invasion of the CNS by the virus [6].

HIVE is caused mainly by HIV-1 and reported prevalence range from 20% - 60% [7]-[14]. It may be static in which case the encephalopathy is unchanging or progressive where it is associated with neuroregression. HIVE is a severe form of the disease as it constitutes an AIDS defining illness [15] but may be present before significant immunosuppression. According to the Centre for Disease Control (CDC), encephalopathy must include criteria in at least one of the following areas for at least 2 months in the absence of a concurrent illness: 1) failure to attain, plateau or loss of developmental milestones or loss of intellectual ability, 2) impaired brain growth or acquired microcephaly and/or 3) acquired symmetric motor deficit which clinically may manifest as paresis, pathological reflexes or gait disturbances [15].

Delays in acquiring early motor and language skills have been reported as specific neurodevelopmental delays among young children with HIVE, [16] [17] [18] while in older children, decreased language ability, specific cognitive deficits like verbal and memory impairment and challenges with visual-spatial integration and executive function have been reported [19] [20].

Recent neuroimaging studies with quantitative magnetic resonance imaging (MRI) techniques reveal better understanding of the underlying neurobiology of the primary effects of HIV on the developing brain. Findings of Ackermann *et*

al. show white matter abnormalities that indicate that CNS infiltration occurs at an early age among young children initiated on HAART under 3 months of age [21]. These abnormalities are much more subtle than the global cerebral atrophy and or basal ganglia calcifications which are more typically described in the context of children with HIV encephalopathy (HIVE) [22]. In addition, two recent studies have reported subtle white matter microstructural abnormalities [23] and neurochemical abnormalities [24] in relatively well older children. In particular, Hoare *et al.* reported an association between poor performance on tests of executive function and attention with reduced white matter integrity in the corpus callosum in "slow-progressor" children who were considered too well to require ART.

Methods such as those described above, which can detect more subtle changes in especially white matter integrity, may be key in the investigation of both the timing and natural history of neurological complications of HIV. However, despite this emerging literature, there remains a paucity of data from low and middle income countries (LMIC) where the utility of these investigations in a clinical context with high burden of disease, but limited resources and consequent different standards of care remains inadequately explored.

While substantial numbers of children have benefitted from antiretroviral treatment (ART), significant barriers to early ART initiation continue to exist, compared to adults infected with HIV. This places untreated children at risk, particularly of central nervous system (CNS) sequelae. HIV-1 invades the developing CNS earlier and with greater severity than observed in adults [7]-[14]. In addition, patients on ART, especially when initiated late, may remain vulnerable to the effects of HIV on the brain because the CNS may be a reservoir for persistent viral replication [16].

In this study, we report the prevalence of HIVE among children with HIV at the University of Port Harcourt Teaching Hospital, mode of transmission of HIV and associated comorbidities.

2. Methodology

This was a retrospective study carried out from January to June 2017. The Research and Ethics Committee of the University of Port Harcourt Teaching Hospital (UPTH) gave approval for the study. The case notes of all HIV positive children who presented to the Consultant Paediatrics Clinic (CPC), Children Emergency Ward (CHEW) and Children Medical Wards (CHMW) of the University of Port Harcourt Teaching Hospital (UPTH) were retrieved. Children with the diagnosis of HIVE who met the diagnostic criteria for HIVE according to the Centre for Disease Control (CDC) definition were selected. CDC definition criteria for HIVE include at least one of the following criteria for at least 2 months in the absence of a concurrent illness: 1) failure to attain, plateau or loss of developmental milestones or loss of intellectual ability, 2) impaired brain growth or acquired microcephaly and/or 3) acquired symmetric motor defi-

cit-which clinically manifest as paresis, pathological reflexes or gait disturbances [15]. The socio-demographic characteristics of the patients, mode of HIV transmission, CD4 count in the last six months, comorbidities and documented diagnostic criteria for HIVE were retrieved from the case notes. CD4 count was classified using the WHO criteria for immunosuppression while diagnosis for the comorbidities was made using standard diagnostic criteria. Obtained data was analyzed using Epi Info version 7.2 and presented as prose, tables and figures in simple proportions. Comparisms of subgroups carried out using the chi square test while statistical significance at 95% confidence interval were p value < 0.05.

3. Results

A total of thirty five out of the 196 HIV positive children presenting to the hospital were diagnosed to have HIV encephalopathy (HIVE) giving a prevalence rate of 17.9%. Of these 35 children, 18 were males and 17, females giving a male to female ratio of 1:1. The ages of the children ranged from 1.3 to 14 years with a mean age of 5.7 ± 3.1 years. The mean age for the males was 6.4 ± 3.2 years and 5.0 ± 2.8 years for the females. There was no statistically significant difference observed between the sexes (t = 1.35, $p = 0.187$). Table 1 shows the ethnicity of the study group. The Ijaw [15 (42.9%)] and Ibo [12 (34.3%] tribes were most represented. Thirty (85.7%) of the patients with HIVE were on HAART at diagnosis. The mean age at diagnosis of HIV was 3.2 ± 3.1 years and the mean age at diagnosis of HIV encephalopathy was 3.4 ± 3.2 years. The documented route of transmission for all the subjects was mother-to-child-transmission (MTCT). Seventy five percent of the children were breastfed from birth and at 6months all the mothers had discontinued breastfeeding. Figure 1 shows the various co-morbidities found in the study subjects. Tuberculosis was the most prevalent co-morbidity occurring among the patients. The mean CD4 count was 1053 ± 630 cells/ml. Only thirty one (88.6%) of the patients with HIVE had documented CD4 counts in the previous six Months, of these, only 4 (13%) had severe Immunosuppression as shown in Figure 2. Table 2 shows the various criteria for

Table 1. Ethnicity of study group.

Tribe	Frequency (N)	Percent (%)
Bini	1	2.9%
Efik	3	8.6%
Hausa	1	2.9%
Ibo	12	34.3%
Idoma	1	2.9%
Ijaw	15	42.9%
Yoruba	2	5.7%
Total	35	100.0%

Table 2. Criteria for diagnosis of HIV Encephalopathy.

Criteria for diagnosis	Frequency (N)	Percentage (%)
Loss of milestones	3	8.6
Plateau of milestones	5	14.3
Failure to attain milestones	6	17.1
Loss of intellectual ability	2	5.7
Acquired microcephaly	31	88.6
Paresis	1	2.9
Pathological reflexes	4	11.4
Gait disturbances	1	2.9

**Many children had more than one criterion.

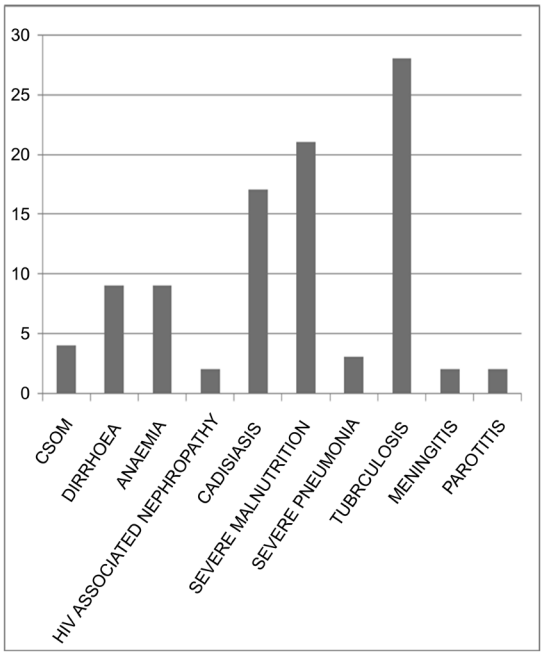

Figure 1. Co-morbidities among study subjects. **CSOM-Chronic suppurative Otitis media.

making the diagnosis of HIV encephalopathy identified in the records of the subjects. The most prevalent was acquired microcephaly (88.6%).

Table 1 shows the ethnicity of the study group. The Ijaw [15 (42.9%)] and Ibo [12 (34.3%] tribes were most represented.

Table 2 shows the various criteria for making the diagnosis of HIV encephalopathy identified in the records of the subjects. The most prevalent was acquired microcephaly (88.6%).

Figure 1 shows the various co-morbidities found in the study subjects. Tuberculosis was the most prevalent co-morbidity occurring among the patients.

Figure 2 shows the levels of immunosuppression of the study subjects based on CD4 count. Thirty one (88.6%) out of those with HIVE had documented

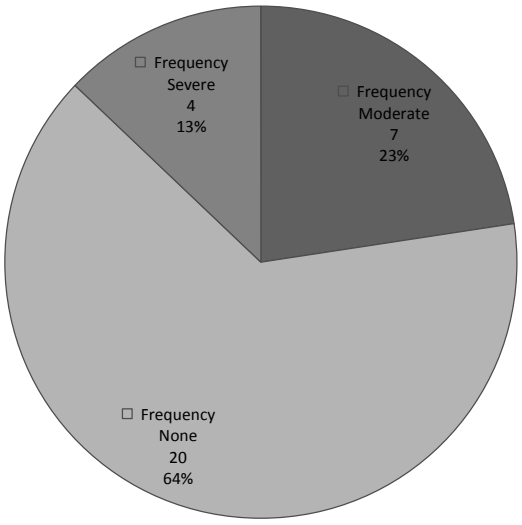

Figure 2. Level of immunosuppression based on CD4 count.

CD4 count in the previous six months. Of these, only 4 (13%) had severe Immunosuppression.

4. Discussion

This study show that HIVE is common in UPTH, but the observed prevalence of 17.9% is low compared to other studies [7]-[14]. It is possible that there areun-diagnosed cases as the diagnostic criteria in this study was mainly clinical. Other studies with higher prevalence revealed sub-clinical cases with white matter abnormalities using neuroimaging studies [23] [24]. The fact that a great proportion (85.7%) of the patients were on HAART at diagnosis of HIVE may also contribute to the lower prevalence as prevalence of 10% - 20% have been reported among children on HAART, this is especially so when HAART was commenced early. However, in this study, it is not known if these children had developed HIVE before HAART was commenced but what is obvious is that at diagnosis of HIVE they were already on HAART. This brings to fore the need for early infant diagnosis (EID), early and prompt initiation of HAART in children and infants with confirmed HIV disease since the CNS is a known sanctuary site for HIV replication. Also, early CNS invasion in HIV disease before the onset of severe immunosuppression is well documented as cases of HIVE in children initiated on HAART as early as three months have been reported [21]. The need for the availability of modern diagnostic neuroimaging technique that detects early subtle changes in the CNS and early prompt initiation of HAART need not be overemphasized.

There is an equal sex ratio in this study as reported in many other studies. Sex has not been shown to contribute to significant changes in reported prevalence of HIVE as was found in this study. However, HIVE occurred at an early age among females than males in this study possibly suggesting that females may be more prone to early CNS invasion than males. This requires further study with a

large population.

Residents of Port Harcourt are mainly individuals of the Ijaw and Ibo tribes as is represented in the study population. Ethnic variation in HIV disease has not been reported though some genetic markers have been shown to protect against HIV disease. However, these genetic markers have not been shown to have ethnic links.

The route of transmission was vertical in 100% of the patients and this is in tandem with most Paediatric HIV/AIDS infection where 95% or more are due to MTCT. The fact that in 100% of the children breastfeeding was discontinued at six months showed that transmission of HIV was early in most of them (because they all had vertical transmission), however, the mean age at diagnosis of HIV and HIVE in these children were 3.2 ± 3.1 and 3.4 ± 3.2 years respectively. This shows that there is limited acute search for children infected with HIV and its complications in this centre and reinforces the need for early infant diagnosis and modern diagnostic tool for early detection of HIVE. Early detection and commencement of HAART in young children have been found to reduce cognitive impairment associated with HIVE.

As at 2017, the National breastfeeding policy in Nigeria for children born to HIV positive mothers stipulates exclusive breastfeeding for six months and then commencement of complimentary feeding with continued breastfeeding and subsequent discontinuation of breastfeeding at one year. However, individuals who opt for exclusive breast milk substitute and can afford, sustain and make it safe for their children are counseled and supported. This policy is so because the risk of dying from prevalent infectious diseases like diarrhea and pneumonia in non-breast fed infants is higher than that of dying from HIV disease at this early age. Studies have also shown that effective prevention of MTCT can take place in children who are breastfeeding. In this study, however, all the mothers had stopped breast feeding at six months showing poor health worker education and communication skills. It also reflects the poor health seeking behavior that is rife among our population.

In children with HIV, CD4 cell countis used for immunological classification and to monitor response to treatment after commencement of HAART. It varies with age, usually higher in the younger age until about five years when it assumes the adult values. **Table 3** shows the WHO classification of immunosuppression using the CD4 cell count.

In this study, 64% of the patients with HIVE had no immunosuppression. Although HIVE is an AIDS defining illness, studies have shown that many patients develop HIVE in the absence of significant immunosuppression as was found in this study [15]. This is thought to be due to the early invasion of the CNS by the virus in children and the fact the CNS act as a sanctuary site for viral replication [7]-[14] [16] [21]. However, this CD4 count may also reflect an immunological improvement following commencement of HAART in these children since all the children were already on HAART at diagnosis of HIVE.

Table 3. WHO classification of immunosuppression using CD4 counts.

HIV disease category	CD4 0 - 12 months old	CD4 1 - 5 years old	CD4 6 - 12 years old
Category 1—no damage	over 1500	over 1000	over 500
Category 2—moderate	750 - 1500	500 - 1000	200 - 500
Category 3—severe	Less than 750	Less than 500	Less than 200

The diagnostic criteria for HIVE in nearly 90% of the children were acquired microcephaly. This is a condition in which a child's head circumference is within the normal range at birth and for an undefined period thereafter but then does not increase as fast as normal and as a result, crosses below the second percentile [25]. Recognized causes include familial, Downs syndrome, Rett Syndrome, Angelman syndrome and acquired brain injury. Any of the diagnostic criteria for HIVE according to the CDC definition may be used for diagnosis, but in these patients, acquired microcephaly was the commonest feature identified. It is possible that this may be an early manifestation of the disease since this usually results from cerebral atrophy caused by the HIV virus.

Many of the children with HIVE had multiple comorbidities including Tuberculosis (TB), HIV Associated Nephropathy (HIVAN), severe malnutrition and severe pneumonia. Tuberculosis (TB) was the leading comorbidity found in over 90% of these children. This is in keeping with it being the commonest opportunistic infection among children with HIV. Worrisome is the fact that TB is an indicator of severe disease with its onset occurring in children with severe immunosuppression, however many of these children had no evidence of immunosuppression. This is probably due to immune recovery with commencement of HAART in these patients since the CD4 values used to assess the level of immunosuppression was that done in the last six months. Is it possible that TB also sets in HIV patients in the absence of significant immunosuppression as occurs in children with HIVE or that CD4 assay is not a sensitive tool to assess the severity of immunosuppression or a combination of these factors?

5. Conclusion

In conclusion, HIVE is common in children with HIV at the University of Port Harcourt Teaching Hospital and it is associated with many comorbidities especially tuberculosis. Early infant diagnosis and modern diagnostic tool like neuroimaging studies are advocated as this will enhance its early detection, early initiation of HAART and reduction in associated morbidity and comorbidity.

Financial Sponsorship

The article is sponsored by the authors.

Conflict of Interest

There is no conflict of interest.

Limitation of the study

The fact that this was a retrospective study poses some limitation to the study as some of the data in the records may not be correct. Also, the small sample size may limit generalization of the findings of this study.

References

[1] Tindyebwa, D., Kayita, J., Musoke, P., Eley, B., Nduati, R., Tumwesigye, N., *et al.* (2011) Handbook on Paediatric AIDS in Africa. 2nd Edition, African Network for the Care of Children Affected by AIDS (ANECCA), Kampala.

[2] UNAIDS (2012) Together We Will End AIDS. 1-140.

[3] WHO, UNAIDS and UNICEF (2011) Global HIV/AIDS Response-Progress Report 2011. 1-219.

[4] Eley, B. (2006) Addressing the Paediatric HIV Epidemic: A Perspective from the Western Cape Region of South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **100**, 19-23. https://doi.org/10.1016/j.trstmh.2005.04.015

[5] (2007) Western Cape Department of Health: Revision of the Protocol for the Prevention of Mother-to-Child Transmission of HIV. Circular No: H127/2007.

[6] Van Rie, A., Harrington, P.R., Dow, A. and Robertson, K. (2007) Neurologic and Neurodevelopmental Manifestations of Pediatric HIV/AIDS: A Global Perspective. *European Journal of Paediatric Neurology*, **11**, 1-9. https://doi.org/10.1016/j.ejpn.2006.10.006

[7] Lobato, M.N., Caldwell, M.B., Ng, P. and Oxtoby, M.J. (1995) Encephalopathy in Children with Perinatally Acquired Human Immunodeficiency Virus Infection. Pediatric Spectrum of Disease Clinical Consortium. *The Journal of Pediatrics*, **126**, 710-715. https://doi.org/10.1016/S0022-3476(95)70397-7

[8] Tahan, T.T., Bruck, I., Burger, M. and Cruz, C.R. (2006) Neurological Profile and Neurodevelopment of 88 Children Infected with HIV and 84 Seroreverter Children Followed from 1995 to 2002. *The Brazilian Journal of Infectious Diseases*, **10**, 322-326.

[9] Blanche, S., Rouzioux, C., Moscato, M.L., Veber, F., Mayaux, M.J., Jacomet, C., *et al.* (1989) A Prospective Study of Infants Born to Women Seropositive for Human Immunodeficiency Virus Type 1. HIV Infection in Newborns French Collaborative Study Group. *New England Journal of Medicine*, **320**, 1643-1648.

[10] Bruck, I., Tahan, T.T., Cruz, C.R., Martins, L.T., Antoniuk, S.A., Rodrigues, M., *et al.* (2001) Developmental Milestones of Vertically HIV Infected and Seroreverters Children: Follow up of 83 Children. *Arquivos de Neuro-Psiquiatria*, **59**, 691-695. https://doi.org/10.1590/S0004-282X2001000500007

[11] Chase, C., Ware, J., Hittelman, J., Blasini, I., Llorente, A., Anisfeld, E., *et al.* (2000) Early Cognitive and Motor Development among Infants Born to Women Infected with Human Immunodeficiency Virus. *Pediatrics*, **106**, e25. https://doi.org/10.1542/peds.106.2.e25

[12] Englund, J.A., Baker, C.J., Raskino, C., McKinney, R.E., Lifschitz, M.H., Petrie, B., *et al.* (1996) Clinical and Laboratory Characteristics of a Large Cohort of Symptomatic, Human Immunodeficiency Virus-Infected Infants and Children. AIDS Clinical Trials Group Protocol 152 Study Team. *Pediatric Infectious Disease Journal*, **15**, 1025-1036.

[13] Epstein, L.G., Sharer, L.R., Oleske, J.M., Connor, E.M., Goudsmit, J., Bagdon, L., *et*

al. (1986) Neurologic Manifestations of Human Immunodeficiency Virus Infection in Children. *Pediatrics*, **78**, 678-687.

[14] Foster, C.J., Biggs, R.L., Melvin, D., Walters, M.D., Tudor-Williams, G. and Lyall, E.G. (2006) Neurodevelopmental Outcomes in Children with HIV Infection under 3 Years of Age. *Developmental Medicine & Child Neurology*, **48**, 677-682.

[15] CDC: 1994 Revised Classification System for HIV Infection in Children Less than 13 Years of Age. *CDC* 1994, **443**, 1-10.

[16] Thomas, S.A. (2004) Anti-HIV Drug Distribution to the Central Nervous System. *Current Pharmaceutical Design*, **10**, 1313-1324.

[17] Van Rie, A., Mupuala, A. and Dow, A. (2008) Impact of the HIV/AIDS Epidemic on the Neurodevelopment of Preschool-Aged Children in Kinshasa. Democratic Republic of the Congo. *Pediatrics*, **122**, e123-e128.

[18] Laughton, B., Cornell, M., Grove, D., Kidd, M., Springer, P., Dobbels, E., *et al.* (2012) Early Antiretroviral Therapy Improves Neurodevelopmental Outcomes in Infants. *AIDS*, **26**, 1685.

[19] Abubakar, A., Van Baar, A., Van de Vijver, F.J., Holding, P. and Newton, C.R. (2008) Paediatric HIV and Neurodevelopment in Sub-Saharan Africa: A Systematic Review. *Tropical Medicine & International Health*, **13**, 880-887. https://doi.org/10.1111/j.1365-3156.2008.02079.x

[20] Laughton, B., Cornell, M., Boivin, M. and Van Rie, A. (2013) Neurodevelopment in Perinatally HIV-Infected Children: A Concern for Adolescence. *Journal of the International AIDS Society*, **16**, Article ID: 18603.

[21] Ackermann, C., Andronikou, S.F., Laughton, B.F., Kidd, M.F., Dobbels, E.F., Innes, S., *et al.* (2014) White Matter Signal Abnormalities in Children with Suspected HIV-Related Neurologic Disease on Early Combination Antiretroviral Therapy. *The Pediatric Infectious Disease Journal*, **33**, e207-e212.

[22] Hoare, J., Ransford, G.L., Phillips, N., Amos, T., Donald, K. and Stein, D.J. (2014) Systematic Review of Neuroimaging Studies in Vertically Transmitted HIV Positive Children and Adolescents. *Metabolic Brain Disease*, **29**, 221-229.

[23] Hoare, J., Fouche, J.P., Spottiswoode, B., Donald, K., Philipps, N., Bezuidenhout, H., *et al.* (2012) A Diffusion Tensor Imaging and Neurocognitive Study of HIV-Positive Children Who Are HAART-Naïve "Slow Progressors". *Journal of NeuroVirology*, **18**, 205-212.

[24] Prado, P.C., Escorsi-Rosset, S., Cervi, M. and Santos, A. (2011) Image Evaluation of HIV Encephalopathy: A Multimodal Approach Using Quantitative MR Techniques. *Neuroradiology*, **53**, 899-908.

[25] Peter, S.B., Alan, S.R., Marianne, H.E.P.D.R. and Ingram, W. (2009) Acquired Microcephaly: Causes, Patterns, Motor and IQ Effects, and Associated Growth Changes. *Paediatrics*, **124**, 590.