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Research Article

Examining a neurodevelopmental problem that affects reading skills: saccadic eye movement abnormalities in children with HIV/AIDS on HAART[1]

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Abstract

Reading is a complex psychological task that involves rapid movements of both eyes in the same direction (saccades) from one word to the next, or, occasionally, backwards to previously encountered text. Eye movement provides a sensitive window into cognitive processing during reading and reading skills are associated with various eye movement parameters, total number of saccades and saccadic amplitudes. This is due to the knowledge that brain areas compromised by HIV infection also control saccadic eye movements. The aim of this study was to investigate the relationship between saccadic eye movements in children with HIV/AIDS on Highly Active Antiretroviral Therapy (HAART). With a descriptive cross-sectional design, 128 conveniently accessed male and female participants of ages 6 years to 13 years 11 months had their saccadic eye movements evaluated. The tool used to screen for saccadic eye movement abnormalities was a numerical reading test called the Development Eye Movement (DEM) test. Descriptive and inferential statistics was developed using SAS. Seventy-eight percent (78%) of participants had minimal immunosuppression and 65% had undetectable viral loads. The DEM test classified participants into four Behaviour Types based on their performances in this timed reading test. Ninety-three percent (93%) had vertical times and 92% had horizontal times that were outside of the specified test norms. The Behaviour Types revealed that 53% had automaticity problems (Type 3), 22% had both eye movement and automaticity problems (Type 4), 8% had no problems (Type 1) and only 3% had eye movement problems (Type 2). The association between the viral load with Behaviour Types (p=0.2) and the CD4 count against the behaviour types (p=0.17) were not statistically significant, hence no relationship could be established. More than half of the sample population manifested automaticity problems. What could not be determined was whether the automaticity problems found in this population were related to the neurocognitive functioning or neurodevelopmental delays which are known to exist in children with HIV/AIDS despite being on HAART, or if it was due to other factors. No relationship could be established between the Behaviour Types specified in the DEM test and the HIV biomarkers despite the DEM performances being largely outside of the standardised norms.

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Introduction

Higher education plays a vital role in promoting students' competence in the world of work. However, the literature Central nervous system (CNS) areas that are involved mediating eye movements can be found in almost every corner of

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the brain (Leigh & Zee, 2006). It is for this reason that value is placed in studying eye movements in different disease states that affect neurologic function. Neurological and mental illness are the most prevalent of chronic diseases and make up approximately 13% of all diseases worldwide (WHO, 2006). Neurological disorders are increasingly prevalent in Sub-Saharan Africa due to various factors of malnutrition, adverse perinatal conditions, malaria, human immunodeficiency virus and the acquired immune deficiency syndrome (HIV/(AIDS) (Silberberg & Katabira, 2006). Clinicians are often challenged to investigate neurological disorders as they are costly, invasive, carries a level of risk and bare a huge economic burden in resource-limited settings in developing countries. There is a constant need to reach early diagnoses through cost-effective, accurate and through non-invasive means (Fitzgerald & Fenniri, 2017). Developing screening tools to identify disease early enough and in a pre-symptomatic stage will support quicker management interventions (Iragorri & Spackman, 2018). Eye movement testing is intrusive yet non-invasive and provides us with a window to the functionalities of the central nervous system. Children represent a vulnerable population as their CNS is developing and susceptible to damage with long-lasting consequences, hence screening tools for early detection with minimal discomfort requires special attention. Early detection, accurate diagnosis and appropriate treatment of HIV-associated neurologic disorders in children often leads to favourable outcomes (Antinori et al., 2013).

Eye Movements with Reading Skill

Reading is a complex psychological task that involves rapid movements of both eyes in the same direction (saccades) from one word to the next, or, occasionally, backwards to previously encountered text (Nikolova et al., 2018). Eye movement provides a sensitive window into cognitive processing during reading (Grace Kim et al., 2022). The relationship between reading skills and eye movement behaviour has been documented in English speaking cohorts. Research in the US with Grade 1 to Grade 3 learners revealed a rapid decrease in temporal eye-movement measure and an increase in spatial eye movement measure in both oral and silent reading. Therefore Krieber et al. (2016) argues that reading skills are associated with various eye movement parameters. It has been found that better reading skills were associated with an increased efficiency in eye movement but were primarily linked to spatial reading parameters such as the number of fixations per word, the total number of saccades and saccadic amplitudes. Studies have found that speed reading was a more reliable predictor for eye movement than reading comprehension. Findings revealed that eye movements where highly correlated across reading tasks which indicates consistent reading performances. Nikolova et al., (2018) believes that fast reading is one of the major skills required for the competent language learner. They argue that it is a matter of training that determines how out eyes moves as quickly as they can be trained to send comprehensive signals to our minds for processing the information in printed material.

Fast reading is one of the major skills required for the competent language learner, although even some native speakers find difficulty in reading fast with full comprehension. It is a matter of training that determines how our eyes move as quickly as they can / are trained, and at the same time send comprehension signals to our minds for processing the information in the printed material.

HAART and the CNS

Progression of HIV to the CNS occurs quite rapidly and during the early stages of infection where the virus remains in the CNS compartment (An et al., 1999; Lindl et al., 2010). Neurologic preservation through viral suppression and elevated immunologic function are some of the key outcomes of antiretroviral therapy. Although Highly Active Anti-Retroviral Therapy (HAART) are effective at eradicating the virus from specific bodily systems, children still continue to exhibit HIV-related neurocognitive decline. There is mounting evidence that Highly Active Anti-Retroviral Therapy (HAART) can control the disease but not eliminate it, especially from the CNS which acts as a sanctuary site due to the blood-brain barrier (Albright et al., 2003). Even in the presence of HAART the pathological features of HIV encephalitis do persist, as was found through post-mortem analysis (Gelman et al., 2013; Masliah et al., 2000). Infected children on HAART are able to sustain their ability to function within normal limits and succeed in school but are at high risk for developmental delays and may exhibit deterioration in the major domains of cognition, speech/language, motor functioning abilities (Boissé et al., 2008) working memory (Bisiacchi et al., 2000), processing speed and other executive functions (Haase et al., 2014). Unfortunately, insufficient scientific information exists regarding the neurocognitive strengths and weaknesses in infected children and adolescents on HAART (Martin et al., 2006) with

limited research on eye movement abnormalities in the paediatric population in this HAART era with no known established relationship to immunosuppression.

Biomarkers of HIV infection

A CD4 cell count is an immunologic biomarker that is a direct indicator of how healthy the body's immune system is (Garcia & Guzman, 2022) with >500cell/mm^3 indicating a healthy immune system. The HIV viral load (VL) is the best indicator of how active the virus is in the blood. Viral load testing is a useful predictor of clinical disease progression (Oliveira et al., 2010). These two parameters however do not share a distinct inverse relationship but demonstrate a modest to poor correlation as some patients can have an undetectable viral load but with a weakened immune system (Mellors et al., 1996; Mofenson et al., 1997). A meta-analysis of five Paediatric AIDS Clinical Trials Group studies have shown that viral load and not CD4 counts were predictive of cognitive decline in children beyond the infancy stage (Lindsey et al., 2000) whereas Shanbhag et al (2005) demonstrated that viral load and CD4 count are marginally predictive of neurocognitive testing outcomes (Shanbhag et al., 2005). The viral load and CD4 count are independent predictors of disease progression and mortality risk but with the combined use of these two biomarkers, prognosis of infected individuals can be more accurately determined (Langford et al., 2007; Palumbo et al., 1998).

Eye movement studies in different disease states

The study of eye movements has been a useful source of information to clinicians and scientists, where specific functional impairments provided information about the location of an active disease process and to monitor of existing disorders or diseases (Leigh & Zee, 2006). Over the past three decades, eye movements have been used as an experimental screening tool to gain insight into AIDS-related diseases, learning-related disorders, psychiatric disorders, neuromuscular disorders, fetal alcohol spectrum disorders and neurological disease. (Bittencourt et al., 2013; Green et al., 2007; Jaafari et al., 2011; Nerušil et al., 2021; Shmukler et al., 2021). Due to the overlap between brain areas that mediate saccadic eye movement function and that which are injured by HIV persistence, specifically the basal ganglia and deep white matter (Boissé et al., 2008) saccadic eye movement testing may provide valuable insight into CNS of people diagnosed with HIV/AIDS. All of these studies reporting eye movement dysfunctions in HIV/AIDS subjects were in the pre-HAART era where there was limited to no control viral replication, hence the need for eye movement research in the HAART era which currently remain scarce. Saccadic eye movement screening has contributed significantly to other areas of human biology in the understanding of disease processes. For this reason, it is thus prudent to investigate the value and reliability of this tool in contributing knowledge in HIV/AIDS pathogenesis.

Screening for saccadic eye movements abnormalities

Screening for eye movement abnormalities that form part of a basic optometric examination (Adhikari et al., 2013; Bilbao & Piñero, 2021) has the potential to provide evidence in support of further investigation and management through early referral. Saccadic eye movements are rapid eye movements that occur to align the visual axes of both eye with objects of interest where the eyes make a conjugate movement to jump from one object to the next (Johnston & Everling, 2008). Typically, about three saccadic eye movements are made every second in everyday life without even being aware of it (Rayner, 1998) making it the most common type of eye movement action that we voluntarily and involuntarily use in everyday life.

Eye movement evaluations are traditionally done by gross observation through induced motility tasks with rating scales to grade the eye movements (Bilbao & Piñero, 2021). In a clinical setting, an alternative to the routinely employed gross observation methods of saccadic testing is the use of psychometric tests that create a reading environment. This class of tests are based on the principle of verbalizing numbers that are read as quickly as possible without the use of a finger to guide the reading (Orlansky et al., 2011). Such tests based on this principle are the Pierce Saccadic Test, the King-Devick Test (K-D), New York State Optometric Association King-Devick Test (NYSOA K-D) test and the Developmental Eye Movement Test (DEM), which was later developed (Orlansky et al., 2011). The Developmental Eye Movement test (DEM) is a simple psychometric test that is recommended as an appropriate oculomotor assessment tool in optometric clinical practice for school-aged children (Tassinari & DeLand, 2005). The DEM test falls into the domain

of Rapid Automatic Naming (RAN) tests where its purpose was to quantify the efficiency of saccadic eye movements based on the speed and accuracy that a series of single digit numbers could be recognized and verbalized (Rouse et al., 2004).

Aim and Problem of the Study

This study aimed to investigate the relationship of saccadic eye movement abnormalities in children with HIV/AIDS on HAART. The objectives pursued to investigate this research inquiry was to determine the prevalence of saccadic abnormalities in children on HAART and if a relationship existed between saccadic eye movement abnormalities and immunologic and virologic biomarkers.

Considering that the saccadic eye movement centres located in the brain are targets sites for HIV-related structural damage, could abnormal saccades be a hallmark indicator of CNS damage from HIV? What further remains elusive is the point at which children would manifest with neurologic or neurocognitive impairment while on HAART and if the presence of abnormal saccades could be associated with the CD4 count and viral load parameters.

Methods

Research Model

A descriptive cross-sectional study design was adopted as data was gathered at a single point in time from the population. This non-interventional study was observational in nature as the characteristics of the data and existing variables helped explain the results obtained through epidemiological methods.

Participants-Sampling

All children were diagnosed with HIV/AIDS and on HAART of ages ranging from 6 years to 13 years 11 months living Free State province in South Africa. All Participants were of African ethnicity and used the home languages of Sotho or Afrikaans but were familiar with English. A sample size 128 participants met the inclusion criteria from 185 children that were accessible to the researcher. Participants were sourced from 8 public health facilities where they were registered at to access their treatment. Inclusion criteria comprised of vertical exposure from mother-to-child-transmission (MTCT), identical ARV regimen, no history of neurological and psychological disorders and excellent ocular health and vision. Participants had to be knowledgeable of numbers. The latest CD4 count, and viral load information was extracted from the health records of each participant from the health facilities. Demographic profiles;

Gender distribution was 48% males (n=61) and 52% females (n=67). The mean age was 10 years and 1 month. The most frequent age group was the 9 year olds 23% (n=30) with the 6 year olds being the lowest amount, 3% (n=4). Home language of subjects varied between Afrikaans, Sotho and/or Twana with 0% having English as a home language.

Data Collection Tool

The Developmental Eye Movement (DEM)

The Developmental Eye Movement (DEM) test was the instrument used due to its non-invasive design to evaluate eye movement performances in children It is a visual-verbal reading test which is less intimidating and similar to a child's experience in his/her school environment where reading activities are done. The DEM test (version 1) was developed by two optometrists, Jack E. Richman and Ralph P. Garzia in 1987. The DEM Test booklet is made up of 4 reading tests. The first is a pre-test to prepare the child for what is expected. This is followed by a Vertical Test A and a Vertical Test B, each of which are made up of 2 vertical rows of numbers to be read out aloud. The final test is a Horizontal Test C made up of 16 rows of horizontally displaced numbers of varying number spacing between each digit. A DEM Score Sheet was used to calculate and record the results of each participant for analysis and interpretation.

Patient Recording Form

A Patient Recording Form was used with each accessible participant. Information recorded was Phase 1 - demographic information and medical history including ARV treatment CD4 count and viral load, Phase 2 - results of the vision screening and eye health assessment results and Phase 3 - DEM Test result. If the patients met the inclusion criteria from the phase 1 and phase 2, they were then included in the study sample to proceed to phase 3 – DEM testing.

Procedure

The researcher was seated next to the participant at a table with the DEM test placed in front of the participant. A room in each of the data collection site was used where there was minimal distraction. The researcher also placed a timer on the table. The researcher provided instruction to the participant in line with the DEM instruction manual. The participant had to first do the DEM Pre-test prior to performing the main DEM test made up of Test A, Test B and Test C. The subject was expected to read out aloud the single digit numbers as fast and accurately as possible on the pre-test without using a finger to visually track the numbers being read out. The participant was not informed that he/she was being timed. The pre-test assured the examiner that the participant was familiar with the numbers and instructions. No recording of time was need with the pre-test. The examiner has the DEM scoresheet placed in front of him to follow what is being read by the participant and mark any errors that was made. The time was recorded written down on the DEM Score Sheet for all of the 3 sub-tests. The duration of the DEM test did not exceed 10 minutes making it least imposing to the participants.

Data Analysis

The raw data from the DEM scoresheet of each participant assessed four components i.e. the Total Vertical Time (TVT), Horizontal Time (HT), Errors and a Ratio score which is determined by taking the horizontal time and dividing it by the vertical time. The DEM allowed adjustment of the HT by taking the errors of omissions and additions into account when computing the horizontal time by presenting an 'adjusted' horizontal time (AHT) as a more authentic computation of the time. These results were then compared against the normative table of established norms of the DEM test according to the chronological age of each participant. (Garzia et al., 1990). Based on the results of the parameters for each participant, the DEM test then approaches to diagnose participants by classifying them into one of four Behaviour Types.

Table 1. List of Behaviour Types and interpretation

Behaviour Type	Vertical Time	Horizontal Time	Ratio	Characteristic
Type 1	normal	normal	normal	Normal automaticity and oculomotor skills
Type 2	normal	high	high	Oculomotor dysfunction only
Type 3	high	high	normal	Deficiencies in automaticity skills only
Type 4	high	high	high	Deficiencies in automaticity and oculomotor skills

Table 2. Non-standardised Behaviour Type that is not specified in the DEM test.

Behaviour Type	Vertical Time	Horizontal Time	Ratio
Type 5	high	normal	Low to normal

The Statistical Analysis Software (SAS) version 9.2 was used to compute the data by the biostatistician from the Faculty of Health Sciences at the University of the Free State. The statistical framework was based on non-parametric assumptions. Descriptive statistics were used to evaluate the categorical and numerical data such as age, gender, time from birth diagnosis, time from diagnosis to treatment initiation, duration on HAART, CD4 count and viral load across the different age groups, mean performances in the DEM per age group, prevalence of Behaviour Types from the sample. Measurements of central tendency was be computed to provide information on the distribution of the data for single variables during a univariate analysis. For the inferential statistics, a correlation analysis was done between the CD4 count and the viral load which was expressed using Spearman's Correlation Coefficient (r). Statistical significance testing between the categorical variables was evaluated using the Fisher's Exact Test. Precision of the estimates were assessed using a 95% confidence interval.

Ethics

An expedited ethics review was requested by the University of Kwa-Zulu Natal Biomedical Research Ethics Committee after submission of the study proposal. This type of review was requested as there were no invasive procedures to be

performed during the data collection process categorising this study as negligible or minimal risk. Permission to use the 8 public health facilities to access the participants, their health records and the use such facilities as the data collection sites was requested from the Head of Health for the Free State province.

A signed informed consent was obtained from the caregivers of all participants. Information sheet and the consent form outlining the research process and patient rights was available in English, Afrikaans and Sotho languages. The anonymity of the participants was maintained as no names were be used in the data collection form, but a code for each subject was allocated. There was a 7-digit code developed for each subject. The confidentiality of the participants' health status and their medical history was also maintained as the knowledge of such was only held by the researcher who was the only data collection personnel along with the nursing staff that provided assistance at the data collection sites.

Results

Biomarker characteristics

The immune status of the sample indicated 5.5% (n=7) of subjects had severe immunosuppression (<200 cell/mm^3), 16.4% (n=21) had moderate suppression (200 – 500cells/mm^3) and 78.1% (n=100) of participants had satisfactorily healthy immune systems with minimal/no suppression (>500 cells/mm^3). The highest mean CD4 count was in the 9-year-olds with 995.77 cell/mm^3 the lowest mean CD4 count in 13-year-olds with 584.54 cells/mm^3. All age groups had a mean CD4 count above 500 cells/mm^3 indicating a healthy sample population. The sample was also categorized according to the viral load parameter with 65% (n=81) had undetectable viral loads, 25% (n=32) had viral loads between 40 – 1000 copies/ml and 10% (n=12) subjects had viral loads exceeding 1000 copies/ml. The median viral load was <40copies/mm^3 indicating an undetectable viral load or adequate viral suppression.

HAART characteristics

The median value for the duration of the sample population on HAART was 2yrs 10 months (34 months) with the minimum being 4 months and the maximum being 6 years and 8 months (92 months). From the period of birth to treatment initiation the median value was 7 years (83.9 months) with the minimum duration of 10 months and maximum duration of 13 years and 6 months (162 months).

DEM test results

When the TVT results for the total sample were compared against the standardized DEM norm, 92.97% of the total participants averaged times beyond (higher) the expected norm. The mean TVT for the vertical tests was 87.85 (±29.19) seconds. The DEM norm was 44.17 (±8.39) seconds. For the AHT, 92.19% of subjects averaged times outside (higher) of the expected norm. The mean AHT was 111.72 (±47.48) seconds. The DEM mean was 57.78 (±14.93) seconds.

Figure 1 shows that the TVT per age catergory were well above the DEM mean norm across all age groups. As the ages of the subjects increased, the performance on the vertical tests improved in both the DEM norm as well as in this study sample. From ages 6 to 9 years, the difference in times is the greatest between the TVT and the DEM norm.

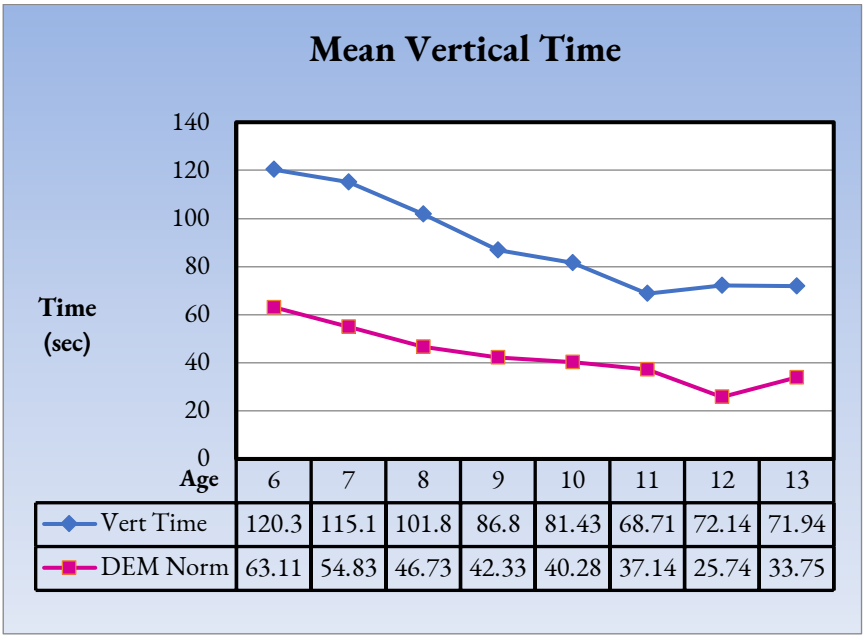


Figure 1. The mean TVT of the study population for each age category is presented with the DEM norm.

Figure 2 shows us that for every different age group, the mean AHT is higher than the DEM norm. The mean AHT decreases with age as the participants whom are older perform the test faster. From 9 years old, the difference in mean times between the age groups is decreased and reached a plateau. From the 6 to 9 year olds, there is a large difference in the mean times in those age groups.

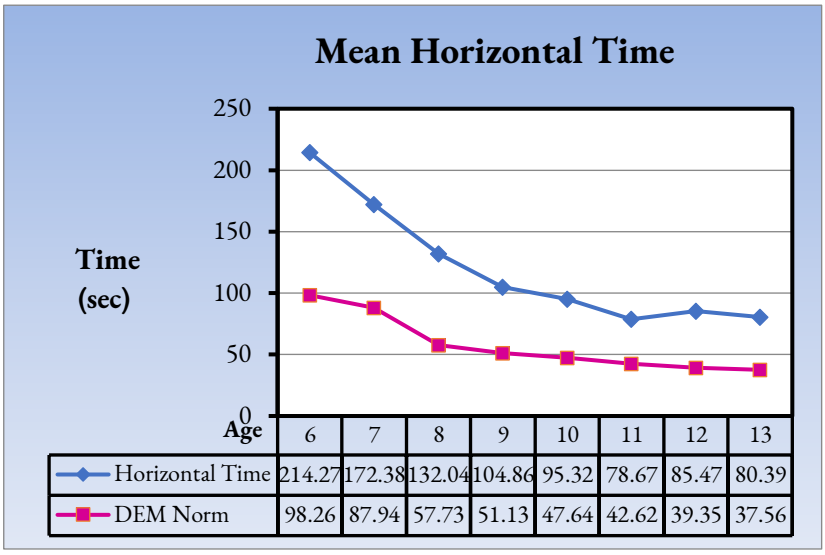


Figure 2. The mean AHT from the study population versus the DEM norm.

The mean Ratio Score was 1.27 with 55% of the total sample falling within the mean of DEM norm and standard deviation. The DEM norm for the ratio score was 1.28. Except for the 6-year-old age group, the other 7 age groups had Ratio scores that where within range of the DEM norm.

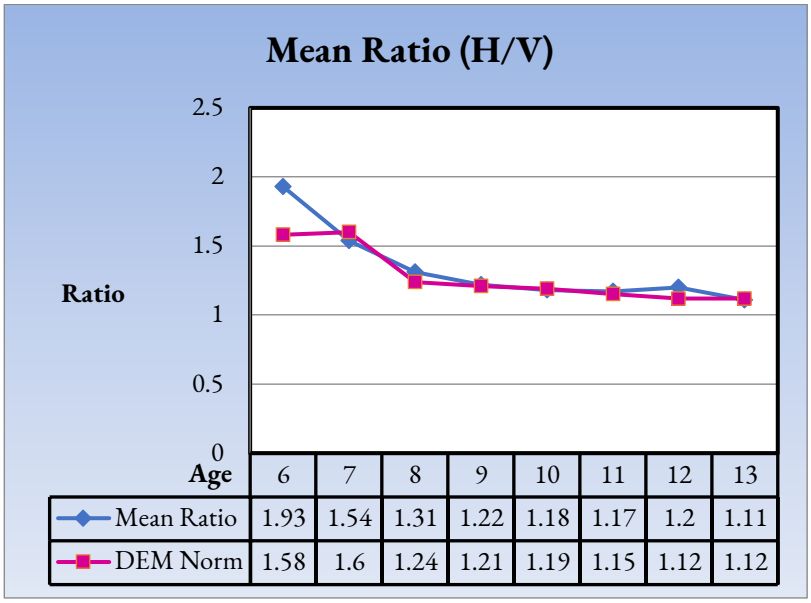


Figure 3. Mean ratio score per age group in this study versus the DEM ratio norm.

Behaviour Types Classification of the participants

Behaviour Type prevalence showed that 53% (68) of the subjects were classified as Behaviour Type 3 (Automaticity problems), 22% (28) were Behaviour Type 4 (Automaticity & Oculomotor dysfunctions), 8% (10) were Behaviour Type 1 showed normal findings, 3% (4) were Behaviour Type 2 (oculomotor dysfunction) and 14% (18) were unspecified type. A surprising 14% (18) of subjects fell into an unspecified category of behaviour types. The distinct characteristic of this type 5 is the low ratio. Of the 18 subjects in this category, 13 had increased horizontal and vertical times displaying similar characteristics to type 3 and type 4 but with a low ratio outside of the norm for those participant's age.

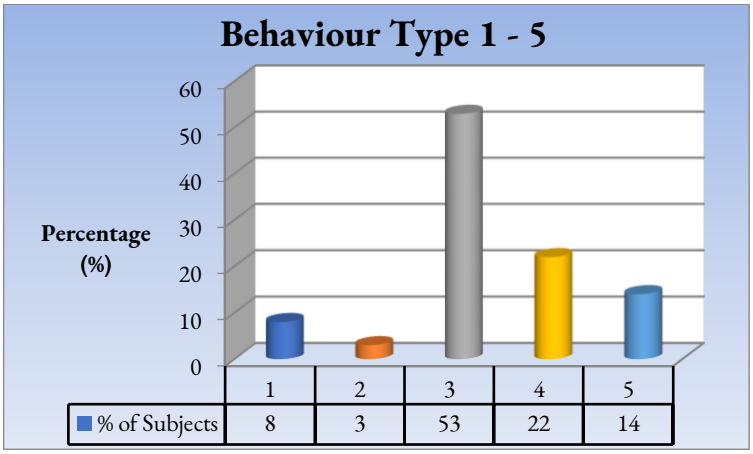


Figure 4. Percentage of subjects classified into the different behaviour types from 1 – 5.

In pie chart (a) displaying the behaviour trends in 6 year old subjects, the only behaviour types that are present is behaviour type 2 and behaviour type 3. The sample size (n) in this age category is only four which then means that one of the four exhibited pure oculomotor dysfunction. In pie charts (b) – (d), the behaviour type 2 once again featured as the smallest percentage of the pool but yet again still represented only one subject. The reason the percentage of behaviour type 2 decreased with age is because the sample pool in the different age categories increased from 13 in 7 year olds, 24 in 8 year olds and 30 in 9 year olds. Consistently, it was noted that behaviour type 3 made up no less than 57% of the sample in the different age categories. Behaviour Type 5 (light blue) featured at the age group 9 category representing 6 of the 30 subjects in this age group. In pie chart (e) – (h) there is an absence of behaviour type 2 (red) from the 10 year old age group where we see the 1st appearance of Behaviour type 1 (dark blue) which is the normal behaviour types. There is a progressive increase with normal behaviour types from the 10 year old age group to the highest prevalance found in the 13 year old age group.

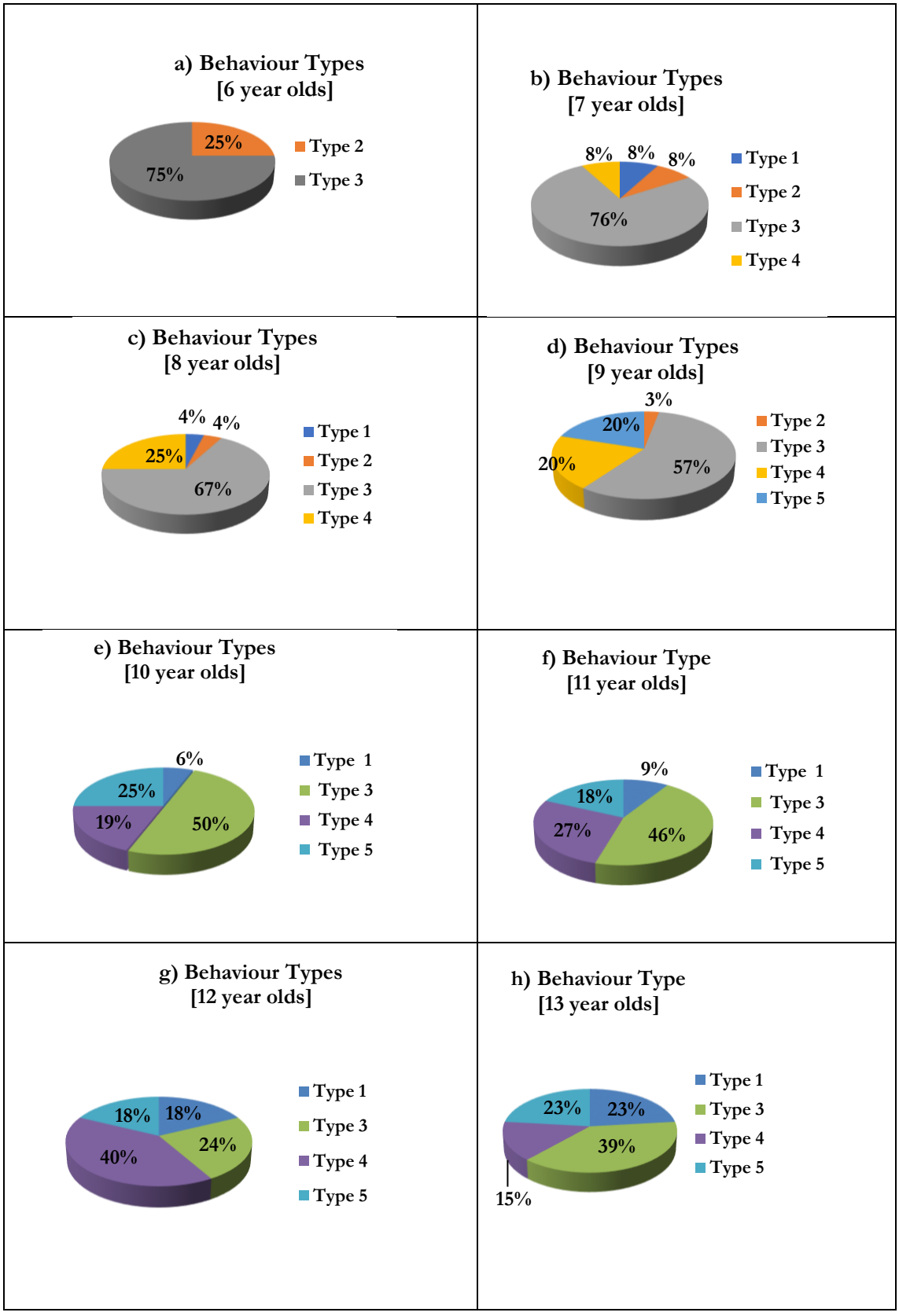
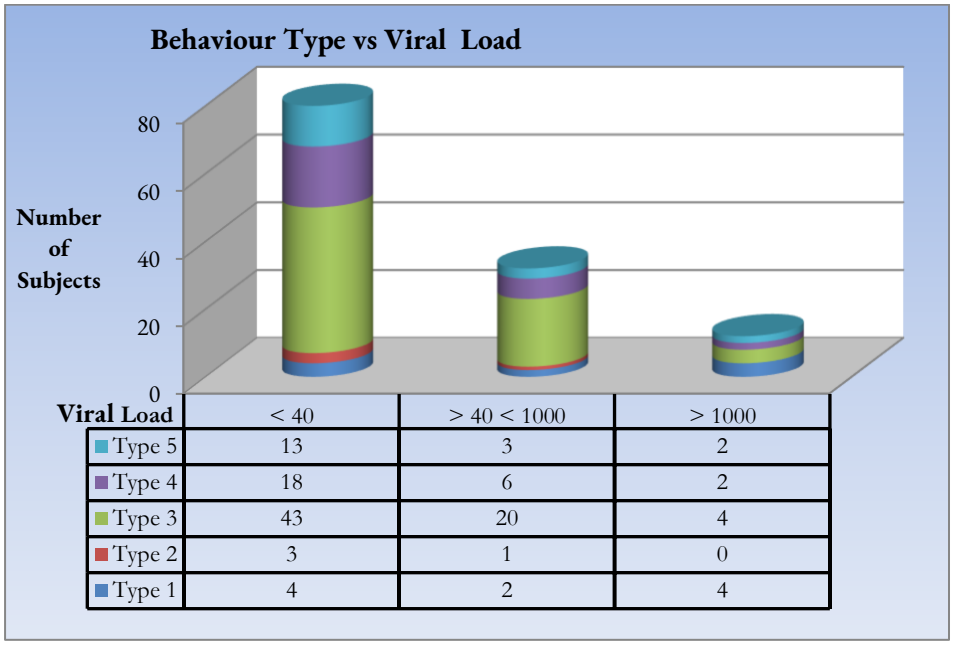


Figure 5. A presentation of the behaviour type prevalences in the age groups 6 – 13 years old.

Each cylinder comprised of the different Behaviour Types that is prevalent in the three virologic categories. The data table showed that with a very high percentage of 65% of the participants having an undetectable viral load (n = 81), this skewed the data where most of the Behaviour Types where prevalent in this group except for an outlier in Behaviour Type 1 with 4 participants in the high viral load category equalling the same number of participants in the undetectable viral load category. The prevalence of the Behaviour Types from 2 to 5 decreased from the undetectable viral load

category to the virologic failure category. Behaviour Type 3 (green) is the most prevalent type in all three virologic categories. Behaviour Type 2 (red) is the least prevalent and is absent in the high viral load category.

Significance of association between the viral load and the Behaviour Types with a 3 x 5 Chi Square analysis indicated poor reliability as 53% of the cells had expected counts that were less then 5. The Fisher's Exact test was conducted with n = 125, and $p > 0.05$. The precise determined was *p-value* = 0.2. The *p-value* indicated that there is weak evidence against the rejection of a null hypothesis, hence the null hypothesis was accepted. This indicated that there was no statistically significant difference between the categories of the behaviour types and the viral load.

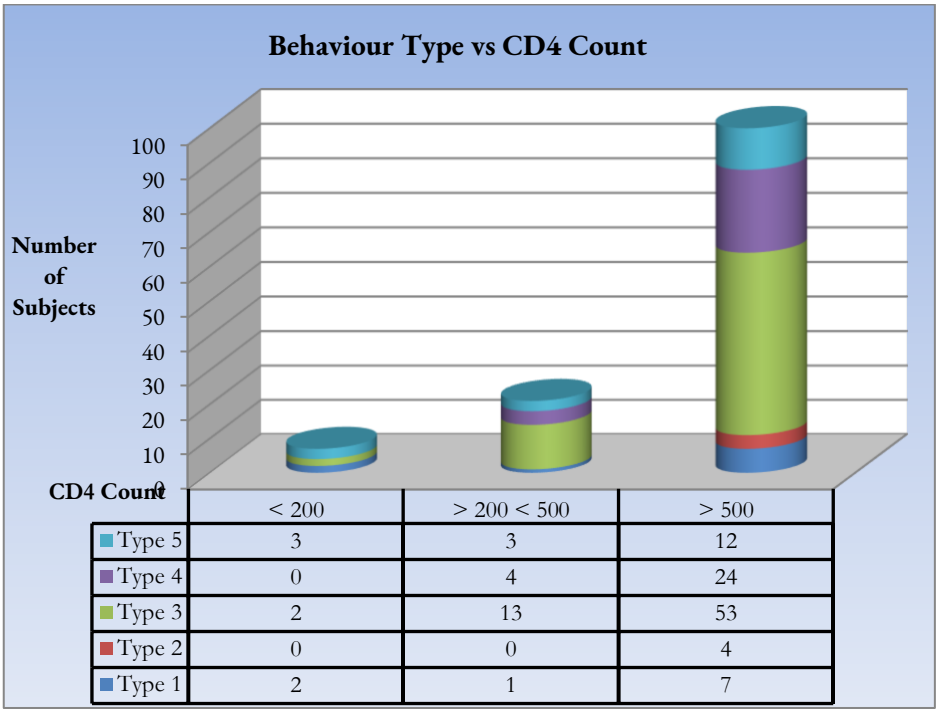


Viral Load	< 40	> 40 < 1000	> 1000
Type 5	13	3	2
Type 4	18	6	2
Type 3	43	20	4
Type 2	3	1	0
Type 1	4	2	4

Figure 6. A presentation of the prevalences of the different behaviour types in the three virologic status categories of the sample

In Figure 6, each cylinder comprises of the different Behaviour Types found for participants in the three immunologic categories. The number of participants classified with the different Behaviour Types in the 3 immunologic categories are found in the data table. Participants with minimal or no immune suppression (>500 cells/mm^3) were in the category with the highest number of subjects that reached 78% (n = 100). This skewed the data where most of the Behaviour Types had the higher prevalence in this group because of the largest proportion of the sample located in that immunologic category. It was observed that Behaviour Type 3 (green) is most prevalent in this sample population with the highest number found in the healthiest immune category.

Significance of association between the CD4 count and the Behaviour Types with a 3 x 5 Chi Square contigency table indicated that 67% of the cells had counts less than 5 so the use of the Chi square test in this case was not valid. The Fisher's Exact test revealed with n = 128, $p > 0.05$, the precise *p-value* = 0.17. This *p-value* indicated that there is weak evidence against the rejection of a null hypothesis. This indicated no statistical significance between the categories of the Behaviour Types and the CD4 count variables.



CD4 Count	< 200	> 200 < 500	> 500
Type 5	3	3	12
Type 4	0	4	24
Type 3	2	13	53
Type 2	0	0	4
Type 1	2	1	7

Figure 7. A presentation of the Behaviour Types in the three immunologic status categories

Discussion

With almost a quarter (23%) of the sample being 9-year-old participants, only 4 were from the 6 to 6 years and 11-month-old category. The reason for a small sample of 6-year-old children was because they were largely illiterate and moderately familiar with verbalizing numbers and these factors excluded them in line with the exclusion criteria. Even though it is noted in the health records that the mode of infection amongst all subjects in the sample is from mother-to-child-transmission, there is no guarantee that horizontal modes of infection are not possibilities. Such modes of transmission include sexual abuse, iatrogenic transmission from hospitals or clinics and receiving of breast milk from HIV positive mothers who are not the biological mothers (Brody, 2003).

Analysis of the CD4 count results and the viral load revealed that a significant proportion the participants in this sample are largely "healthy" with adequate viral suppression and immunocompetent levels. This can be largely attested to the HAART. The reasons for virologic failure in participants on HAART could range from poor treatment adherence to failure of the initial drug regimen resulting in viral rebounding due to activation of latent viral reservoirs. Poor adherences in children are due to many social and psychosocial reasons, which make compliance more difficult with children than with adults. A study by Haberer and Mellins (2009) that looked at paediatric adherence found that child characteristics differ from caregiver characteristics with non-adherence to treatment resulting in failure of HAART (Haberer & Mellins, 2009).

The vertical and horizontal times of the DEM test were distinctly slower across all age groups in this sample when compared to the specified DEM norm. However, the mean ratios and the mean errors were within the specified norms. There are many intrinsic and extrinsic causative factors that may have contributed to the overall slower times. Blanchette et al (2002) indicated that in specific areas like information processing speed, there may be subtle deficiencies within this population, which is a plausible cause for the subnormal rates in both vertical and horizontal tests (Blanchette et al., 2002). Puthanakit et al (2010) studied neurocognitive function in Thai children aged 6 to 12 years using the Welscher Intelligence Scale for Children III (WISC III) and showed that neurocognitive functioning in HIV-infected children on HAART are lower than that of non-infected children (Puthanakit et al., 2010). A study by Martin et al (2006) concluded that HIV-infected children on HAART functioned within normal limits in certain neuropsychological tests, however, differences in performances did exist between subjects with varying levels of brain neuroimaging abnormalities

(Martin et al., 2006). This study emphasised the importance of incorporating neuropsychologic assessments as part of medical care in children with HIV/AIDS.

Other intrinsic factors relate to the neuropathogenesis of the disease and how effective HAART is in controlling CNS viral load, which this study had limited insight into due to inadequate research in these areas of paediatric HIV neuropathogenesis within the African population. The reversal of neuropathologic deficits in infected children on HAART still remains unclear as studies by Chirboga et al (2005) and Lindsey et al (2007) showed modest improvement whereas a study by Nozyce et al (2006) showed persistent mild behavioural and cognitive impairment in the presence of HAART (Chiriboga et al., 2005; Lindsey et al., 2007; Nozyce, 2006).

Extrinsic factors which may have contributed to a sub-standard performance demonstrated by the DEM test results, relate to the social environment and educational support that may have influenced the neurodevelopment and cognitive potential of the subjects. Most of the subjects in this study are from rural and semi-rural areas that attend school in those areas and access the public health services. A South African study by Smith et al (2008) using a battery of standardized cognitive tests that described verbal and non-verbal intelligence scores, showed that HIV-infected children on HAART were much lower than those of non-infected children. The study further indicated that neurocognitive development in HIV/AIDS children are influenced by their socio-economic factors, poor household educational stimulation and nutritional profile (L. Smith et al., 2008).

None of the 128 subjects used English as their home language. The home languages of the subjects were Sotho and Afrikaans. However, English was used in school along with Afrikaans, Sotho and Tswana during the teaching process and informal communication outside of the classroom. One of the possibilities of reduced rates in the DEM test was that the test was conducted in English and the children had to verbalise the numbers in English. Information processing delay may have contributed in part to reduced horizontal and vertical times. The DEM test has standardised norms developed with American children. The participants in this study are all non-English speaking learners and all were from poor socio-economic backgrounds. Fernandez-Velazquez and Fernandez-Fidalgo (1995) from their study on Spanish-speaking norms concluded that the DEM is a reliable tool independent of language differences (Fernandez-Velazquez & Fernandez-Fidalgo, 1995). However, Pang, Lam and Woo (2010) proposed DEM norms for Cantonese-speaking children and cautioned that population-specific norms must be established to minimise bias caused by factors such as language and education (Pang et al., 2010). Bapista et al (2011) described in their study using the DEM test in Portugese-speaking children that language, educational and cultural differences may influence the performance on the DEM test (Baptista et al., 2011). The implications of the conclusions drawn from the previous studies mentioned above does entertain the possibility that the findings in this current study may possibly have been influenced by similar factors as was experienced in those studies in their different populations, or possibly not.

Behaviour Type 3 was distinctly the most prevalent in the study showing that RAN was a significant problem that was revealed in this population with eye movement dysfunction manifesting in an insignificant proportion of the subjects. Deficient automaticity skills may or may not be due to HIV, however, as described in this study, it does exist within the population of school-aged children with HIV/AIDS on HAART. The causes for the automaticity problems could be multifactorial ranging from pathological to socio-economic factors as was with the overall performance in the vertical and horizontal scores. When behaviour type prevalences were compared to the age variable an apparent age-dependant trend was visible. Subjects with eye movement abnormalities were most prevalent in the youngest age group but reduced as age increased and was absent from 10 years onwards. Normal DEM performances (type 1 behaviours) were absent in the 6-year-old and 9-year-old age groups but increased significantly from 10 years upwards with the highest prevalence in the 13-year-old age group. Deficiencies in automaticity skills or RAN, which were the highest with the 6- and 7-year-olds reduced significantly in the 12- and 13-year-old groups showing that there is a trend towards normality as the subjects aged. These findings were independent of their virologic and immune statuses showing that it had no impact on the trend found as age progressed.

Due to the high prevalence of subjects in these 'healthy' categories, all five behaviour types were most prevalent in these two categories rendering any viable comparison of different behaviour types to different viral load and CD4 count

levels, inconclusive. This finding challenged the notion that subjects with higher viral loads would perform poorer on the DEM test and be symptomatic of eye movement problems. It was found that no subject with type 2 behaviours were found in the category with VL > 1000 copies/mm^3 and 4 of the 12 subjects in this viral load category had normal DEM performances (Behaviour Type 1). A similar result was demonstrated when comparing CD4 counts to different behaviour types as was with the comparison done with viral load. All behaviour types were significantly higher in the single category of minimal immune suppression with CD4 counts > 500 cell/mm^3. Subjects classified as having saccadic eye movement problems (Type 2) were not severely immunocompromised, hence no link between their immune and virologic status to their diagnosis based on the DEM was established. This finding further did not support the expectation that unhealthy and severely immunocompromised subjects would have significantly lower performance rates on the DEM. It also did not support the preconceived notion that there would be a high prevalence of behaviour type 2 subjects in the lower immunity categories. There was no statistically significant difference between the different behaviour types and the CD4 count and viral load categories.

There were no reliable indications of immunologic and virologic biomarkers influencing the performance on the DEM test without a convincing relationship to eye movement problems in this population. A relationship between the performances on the DEM test and the disease biomarkers remains unlinked. The only finding that supports a possible relationship with the DEM performance was that of the age of the subjects with the behaviour type trends. There was a progressive increase in the normal scoring in the DEM test (Type 1) with the ageing of the subjects however, it was still below the established norms. The DEM test showed different behaviour types in the sample population, but it failed to show that those with poorly sustained immune systems and high viral burdens had oculomotor dysfunctions.

The obvious finding that was evident in the study was the significant automaticity deficits of the population. Deficient automaticity skills were the highest across all age groups, but its prevalence decreased with ageing children. Furthermore, children with the longest duration on HAART had higher automaticity and eye movement problems but were in the younger age groups. There was no relationship established between poor automaticity skills and disease parameters of CD4 count and viral load in this study but relationships between these parameters to other neurocognitive functions by other neuropsychological tests have been demonstrated (Martin et al., 2006; A. B. Smith et al., 2008). Efficient automaticity requires good cognitive ability as the DEM test is a visual-verbal test. The essence of the DEM test is that it is patient-reliant, hence it is a subjective instrument. Cognitive functions such as visual memory, visual discrimination, visual information processing, processing speed and verbalisation are important components for performing the DEM Test and these are cognitive-dependant skills. Automaticity problems may a predictor or risk factor of neurocognitive impairment as it is cognitive-dependent. Other neurocognitive testing would need to be conducted to confirm if the findings of the DEM test is a reliable indicator of neurocognitive impairment, which is known to occur in this population. The DEM test has value as a screening tool in a subtest of neuropsychological tests beyond its description as an eye movement test as the dependency of this test is heavily reliant on a series of cognitive skills. A study by Ayton et al (2009) concluded the DEM failed to correlate well with other objective measures of saccadic eye movements to be a reliable test of oculomotor function but that it is an indicator of children at risk of reading and academic delays due to its reliance on cognitive functions such as verbalisation and information processing speed (Ayton et al., 2009).

Strong immunity and low viral load as detected in the blood are not reliable indicators that the CNS is unaffected. Studies by Cysique, Maruff and Brew (2004) and Dore et al (2003) showed that since subjects have been started on HAART earlier, the incidence of HAD reduced but the increase in the prevalence of HAND occurred with increased survival due to HAART(Cysique et al., 2004; Dore et al., 2003). A study by Ruel et al (2012) showed that HIV infected children with good CD4 counts, who were not eligible for HAART, manifested with neurocognitive and motor deficits which then questioned the WHO threshold guideline for eligibility for treatment (Ruel et al., 2012). If eye movement dysfunction is not characteristic in this population of HIV-infected school-aged children on HAART but deficiency in RAN is evident it may be plausible that automaticity skill may be indicator of neurocognitive impairment or neurodevelopmental delays.

The DEM in essence still has validity and reliability as a screening tool in clinical practice as its function extends beyond the detection of eye movement dysfunctions and should be used in parallel with other tests of neurocognitive function that are used by optometrists. Screening of neurocognitive function in a school-aged patient is important for the monitoring of their neurodevelopment and for optimal multi-sensory learning in the HIV/AIDS population of school-aged children and even those unaffected by HIV/AIDS. The question arises as to whether the automaticity problems found with the subjects in this study are due to norms developed by a different population or if it's related to HIV/AIDS with the possible existence of neurocognitive impairments in the current population of subjects. This study supports the suggestion by Martin et al (2006) in emphasising that neuropsychological testing needed to be done in all HIV-infected children regardless of their treatment status. Optometrists need to play a more significant role in screening and referring such children as part of a universal health care approach beyond just the attention to primary visual functions especially when confronted with children with HIV/AIDS on HAART.

Conclusion and Recommendations

Neurologic dysfunction due to persistent HIV in the CNS cannot be predicted from eye movement testing using the DEM test in children with HIV/AIDS on HAART. There was no association found between the Behaviour Types of the DEM test and the immunologic and virologic biomarkers. The prevalence of saccadic eye movement abnormalities in children with HIV/AIDS on HAART was very low. There was a high prevalence of automaticity problems found in this population. This unexpected finding cannot confirm or rule out the presence of existing neurocognitive or neurodevelopmental impairment in this population. Performance in all 3 subtests of the DEM was significantly reduced in all age groups according to the standardised DEM norms.

New norms for a DEM test based on non-English speaking children in a South African population should be established. South Africa is a nation of multiple home languages with diverse cultural backgrounds, it should ideally have standardised norms developed from and for its own population for adoption. This could strengthen the reliability and validity of the results that infer deficits in eye movement and automaticity problems for the South African population.

Since social and educational factors influence performance on neurocognitive and neuropsychological tests, a study using the DEM test to compare children of different social, economic and educational backgrounds beyond language differences, should be undertaken.

The DEM test can be used or tested as part of a battery of neuropsychological tests in school-aged children with vertically acquired HIV to determine if its results are consistent with other neuropsychological tests.

A similar descriptive study with an analytical design should be done by comparing the cognitive ability in performing the DEM test amongst subjects who are treatment-naive HIV-infected subjects, HIV-infected subjects on HAART and an HIV-uninfected control group. A control may be valuable to determine if HIV has a negative effect on a child's eye movements and neurocognitive development that is manifested through the DEM test.

To enhance the accuracy of eye movement testing using the DEM test, instructions relating to controlling of head and upper body movements could be given additionally to the prescribed instructions stipulated in the DEM test manual. If newer tests or modifications for this test are researched, these instructions can be recommended to be included to strength the reliability of the results.

Testing of eye movements in paediatric subjects should ideally be done objectively limiting the variability, improving reliability and repeatability of the results. For research purposes, visual tracking devices using infrared technology can be utilised as instruments of choice for analysing eye movements as the sensitivity of these instruments and objectivity is highly reliable.

As current research has shown that HIV-associated neurocognitive disorders are still persistent in the presence of HAART, children with developing systems are still at risk of CNS disease. In consideration of this, eye care professionals could use this knowledge in clinical practice through specific paediatric tests to screen for and monitor neurodevelopmental anomalies beyond the assessment of just the primary visual functions. In the domain of

neurodevelopmental and neuropsychological testing there are an insurmountable number of tests that are used in paediatric assessments by various health professionals. The DEM test should be emphasised in this specific population along with a battery of other neuropsychological tests that optometrists currently use such as the Tests of Visual Analysis Skills (TVAS), Tests of Auditory Analysis Skills (TAAS), Tests of Visual Perceptual Skills (TVPS) and the Developmental Tests of Visual Motor Integration (Beery VMI). The role of health care providers should be to actively identify at-risk patients to get the appropriate medical attention and rehabilitation that is needed at an earlier stage. This action is critical to prevent children from being handicapped by their condition as HIV-associated neurocognitive disorders could be debilitating. This holistic approach to health care could benefit children with HIV/AIDS in levelling the playing field to allow them the same opportunities, success and achievement as non-infected children.

Limitations

The incompleteness of subjects' health records at certain state health facilities posed a challenge, which resulted in a significant number of candidates being excluded from the study. Pre-existing neurological or neurocognitive disabilities, previous hospitalisation details and the time frame of such were unclear in the documentation. Not all subjects had absolute CD4 counts and CD4 percentage calculations as well as absolute viral load and log unit expressions, which would have made data analysis of these parameters easier and simpler.

All subjects in this study were presumed to have contracted HIV through vertical mother-to-child transmission. Records did not indicate if MTCT was the mode of transmission or if contraction of HIV occurred through different modes beyond the infancy age. However, the mode of transmission of all subjects was accepted to be MTCT during the neonatal age of the subjects for this study. The current caregivers of the subjects were not necessarily the biological mother as most biological mothers were deceased. Accurate and detailed case histories of the subjects were therefore limited.

As this study was a descriptive and not an analytical design, it limited a comparability approach to an HIV-uninfected control group.

There were a limited number of 6-year-old subjects in this study due to poor numeracy skills hence the 6-year-old age category was comparably small to the other age categories.

None of the subjects had any neuropsychological or neurodevelopmental testing done to assess the cognitive state of the subjects prior to this study. This meant that the neurocognitive functioning of the HIV-infected subjects before and after HAART was unknown.

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