UNIVERSIDADE FEDERAL DE MINAS GERAIS
INSTITUTO DE CIÊNCIAS BIOLÓGICAS
PROGRAMA DE PÓS-GRADUAÇÃO EM NEUROCIÊNCIAS

# Avaliação das características neuropsicológicas, comportamentais e de desempenho escolar em uma amostra de infanto juvenis infectados pelo HIV verticalmente

BELO HORIZONTE

2015

GUSTAVO DE VAL BARRETO

# Avaliação das características neuropsicológicas, comportamentais e de desempenho escolar em uma amostra de infanto juvenis infectados pelo HIV verticalmente

Tese de doutorado apresentado ao Programa de Pós-Graduação em Neurociências da UFMG, como parte dos requisitos para obtenção de título de doutor em Neurociências.
Linha de pesquisa: Neurociência clínica

Orientador: Prof. Dr. Vitor Geraldi Haase

Co-orientador: Prof. Dr. Jorge Andrade Pinto

BELO HORIZONTE

2015

UNIVERSIDADE FEDERAL DE MINAS GERAIS
INSTITUTO DE CIÊNCIAS BIOLÓGICAS
PROGRAMA DE PÓS-GRADUAÇÃO EM NEUROCIÊNCIAS

**Avaliação das características neuropsicológicas, comportamentais e de desempenho escolar em uma amostra de infanto juvenis infectados pelo HIV verticalmente**

**Doutorando:** GUSTAVO DE VAL BARRETO

**Orientador:** Prof. Dr. VITOR GERALDI HAASE

**Co-orientador**: Prof. Dr. JORGE ANDRADE PINTO

Tese de doutorado apresentado ao Programa de Pós-Graduação em Neurociência da UFMG, como parte dos requisitos para obtenção de título de doutor em Neurociência. Linha de pesquisa: Neurociência clínica

**Banca de avaliação:**

**Orientador:** _____
Prof. Dr. Vitor Geraldi Haase

**Co-orientador:** _____
Prof. Dr. Jorge Andrade Pinto

**1° avaliador:** _____
Prof. Dra. Ana Paula Almeida de Pereira

**2° avaliador:** _____
Prof. Dr. Alexandre Ferreira Campos

**3° avaliador:** _____
Profa. Dra. Flavia Gomes Faleiro Ferreira

**4° avaliador:** _____
Profa. Dr. Antonio Jaeger

## RESUMO

Barreto, G. V. (2015). Avaliação das características neuropsicológicas, comportamentais e de desempenho escolar em uma amostra de infanto juvenis infectados pelo HIV verticalmente. Tese de doutorado, Programa de Pós-graduação em Neurociências, Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais, Belo Horizonte.

A observação de alterações do funcionamento cognitivo e comportamental nos estudos sobre a infecção pelo HIV é uma das preocupações desde o início da epidemia. O desenvolvimento e popularização da terapia antirretroviral combinada (ARV) representa uma transição epidemiológica importante nos estudos do HIV. A implementação da ARV reduz drasticamente a mortalidade e a evolução da doença; entretanto as suas contribuições para a redução dos prejuízos cognitivos ainda não são claras. Estudos mostram efeitos positivos no funcionamento cognitivo, mas essa relação ainda não está completamente esclarecida na literatura. Após a implementação da ARV, o foco dos estudos relacionados à neuropsicologia do HIV está sendo concentrado em encontrar déficits neuropsicológicos diretamente ligados ao HIV; determinar se o déficit é associado a comorbidades (p. ex. doença psiquiátrica, deficiências nutricionais, uso de drogas, hepatite C, efeitos colaterais do tratamento); explorar as relações entre o déficit neuropsicológico e variáveis da doença (contagem de CD4, biomarcadores do HIV e exames de neuroimagem); e explorar a relação entre o comprometimento neuropsicológico e comportamento. As alterações se manifestam ao longo do desenvolvimento do indivíduo e se apresentam por um padrão de prejuízos inespecíficos, afetando tanto o comportamento quanto a cognição. Do ponto de vista cognitiva o, as alterações se manifestam por prejuízos relacionados, especialmente, às funções executivas e velocidade de processamento. Também são afetadas habilidades como linguagem, inteligência, memória, atenção, habilidades motoras e processamento visoespacial. Com o propósito de investigar quais as características neuropsicológicas, comportamentais e o desempenho escolar, foram estabelecidos

dois objetivos a serem desenvolvidos na presente tese: 1) Quais os prejuízos neuropsicológicos mais observados na população infanto juvenil infectados pelo HIV; 2) Quais as características neuropsicológicas, comportamentais e de desempenho escolar em uma amostra de infanto juvenis infectados verticalmente pelo HIV. No estudo I, é realizada uma revisão da literatura sobre as características neuropsicológicas de crianças, adolescentes e jovens adultos (idade inferior a 24 anos), os padrões de comprometimento observados e as principais funções cognitivas avaliadas. Os resultados mostraram que os domínios mais investigados na neuropsicologia do HIV são a inteligência, funções executivas, atenção, memória, velocidade de processamento e motricidade. De modo geral, os resultados mostram que o desempenho dos participantes HIV infectados é inferior à de populações não infectadas. Os prejuízos são mais proeminentes a medida que os parâmetros de evolução da doença avançam. No estudo II foi realizada uma avaliação neuropsicológica ampla, com 50 participantes entre 8 e 22 anos de idade em tarefas que avaliavam inteligência, funções executivas, atenção, motricidade, memória e desempenho escolar. Os resultados indicaram pior performance no grupo com maior evolução da doença (grupo AIDS) em comparação com os participantes do grupo infectado, mas em estágios iniciais ou intermediários (grupo HIV) e o grupo controle. O estudo III explora as características comportamentais em uma amostra de jovens infectados verticalmente pelo HIV em um questionário padronizado respondido por seus pais e/ou responsáveis. Os resultados mostram que não foram observadas alterações comportamentais nos grupos investigados em comparação com as normas populacionais. O trabalho constitui mais uma evidência dos benefícios que a TARV produz na manutenção dos aspectos cognitivos e comportamentais, uma vez que os prejuízos observados são significativamente menores que os relatados na literatura anteriores ao acesso livre promovido pelo governo brasileiro a partir do ano de 1996. Além disso, os prejuízos cognitivos são sutis e mais proeminentes no grupo em estágios mais avançados da infecção.

**Palavras-chave:** Neuropsicologia, HIV, AIDS, cognição, desempenho escolar, comportamento,

avaliação neuropsicológica.


## ABSTRACT

The changes in cognitive and behavioral functioning within the studies of infection by HIV is a concern since the epidemic began. The development and popularization of combinade antiretroviral therapy (HAART) is an important epidemiological transition in HIV studies. The implementation of HAART dramatically reduces mortality and disease progression; however their contributions to the reduction of cognitive impairments are not yet clear. Most studies show positive effects cognitive functioning, but this relationship is not yet fully elucidated in the literature. After the implementation of HAART, the focus of studies related to neuropsychology of HIV is being concentrated on finding neuropsychological deficits directly linked to HIV; determining if the deficit is associated with comorbid conditions (e.g. psychiatric disease, nutritional deficiencies, drugs, hepatitis C, treatment side effects..); explore the relationship between neuropsychological deficits and disease variables (CD4 count, HIV biomarkers and neuroimaging tests); and explore the relationship between neuropsychological impairment and behavior. The changes are manifested throughout the development and are presented by a pattern of non-specific damage, affecting both the behavior and cognition. The cognitive point of view, the changes are manifested by related losses, especially in executive function and processing speed. Other cognitive functions are also affected as language, intelligence, memory, attention, motor skills, and visuospatial processing. In order to investigate which neuropsychological characteristics, behavioral and academic performance were established two objectives to be developed in this thesis: 1) What are the most neuropsychological impairments observed in juvenile childhood population infected with HIV; 2) What are the neuropsychological characteristics, behavioral and academic performance in a sample of infected juvenile childhood vertically HIV. In study I, it is carried out a literature review on the neuropsychological characteristics of children, adolescents and young adults (age <24 years), the commitment patterns

observed and the main cognitive functions assessed. The results showed that the cognitive domains most investigated in HIV neuropsychology are intelligence, executive function, attention, memory, processing speed and motor skills. Overall, the results show that the performance of HIV infected participants is less than the uninfected population. The losses are the most prominent as the evolution parameters of the disease progressing. In Study II a comprehensive neuropsychological assessment was conducted, with 50 participants between 8 and 22 years of age on tasks that assessed intelligence, executive function, attention, motor skills, memory and school performance. The results showed worse performance in the group with greater progression of the disease (AIDS group) compared with participants in the infected group, but in early stages (HIV group) and the control group. The study III explores the behavioral characteristics in a sample of young people infected with HIV vertically on a standardized questionnaire answered by parents. The results show that no behavioral changes were observed in groups investigated compared with population norms. The work is further evidence of the benefits that HAART produces in maintaining cognitive and behavioral aspects, since the observed losses are significantly lower than those reported in previous literature to open access promoted by the brazilian government from the year 1996. In addition, the cognitive impairments are subtle and more prominent in the group in later stages of infection.

**Keywords:** Neuropsychology, HIV, AIDS, cognition, school performance, behavior, neuropsychological assessment.

**Table of contents**

**List of tables**

**Chapter 1 - Presentation**



**Chapter 2 - Study I**



**Chapter 3 - Study II**



**Chapter 4 - Study III**

**List of figures**

**Chapter 2 – Study I**



**Chapter 3 - Study II**

## Chapter 1 - Presentation

Acquired Immunodeficiency Syndrome (AIDS) is a progressive disease of the immune system characterized by the selective destruction of T cells caused by the Human Immunodeficiency Virus (HIV). Since the epidemic began in the 80's, cognitive and behavioral changes caused by HIV infection are recognized, in particular cortical atrophy (Thompson, Dutton, Hayashi, Toga, Lopez, Aizenstein, & Becker, 2005), reduction of basal ganglia (Aylward, Henderer, McArthur, Brettschneider, Harris, Barta & Pearlson, 1993) and overall reduction in white matter (Chen, An, Zhu, Stone, Smith, Hall & Lin, 2009). Cognitive changes most commonly seen in HIV-infected individuals are related to motor skills, executive function, attention, memory and processing speed (Reger, Welsh, Razani, Martin, & Boone, 2002).

The development and popularization of antiretroviral therapy is an important epidemiological transition in HIV studies. The implementation of Combined Antiretroviral Therapy (HAART) dramatically reduces mortality and disease progression; however their contributions to the reduction of cognitive impairments are not yet clear. Most studies show positive effects of HAART on cognitive functioning (Baldeweg, Catalan, Lovett, Gruzelier, Riccio, & Hawkins, 1995; Cohen, Boland, Paul, Tashima, Schoenbaum, Celentano, Carpenter, 2001; Robertson, Robertson, Ford, Watson, Fiscus, Harp & Hall, 2004;. Suarez, Baril, Stankoff, Khellaf, Dubois, Lubetzki & Hauw, 2001), but some have not found significant effects (Tozzi, Balestra, Bellagamba, Corpolongo, Salvatori, Visco-Comandini, & Narcissus, 2007) and others show only moderate effects on improving cognitive performance (Al-Kindi, Zakzanis and von Gorp, 2011).

The adoption of prophylaxis mother to child (CDC, 2006) and the introduction and widespread access to HAART (Nachman, Chernoff, Gona, Van Dyke, Dankner,

Seage, Oleske & PACTG 219C Team, 2009) in the mid-1990s in developed countries and some developing countries such as Brazil (Kakehasi, Pinto, Romanelli, Ram, Cardoso Tavares & Aguiar, 2008; Matida, Ramos, Heukelbach & Hearst, 2009), represent a radical epidemiological transition.

HAART is the use of a series of medicaments for the treatment of retrovirus infections, especially HIV. As the number of new cases of vertical transmission is reduced and children and adolescents survive longer and reach adulthood, the focus of treatment lies with treatment adherence, drug resistance, quality of life and morbidity associated with the disease such as cognitive and behavioral disorders (Hazra, Siberry and Mofenson, 2010). Neuropsychologically, the most important transition is related to a decrease in the incidence of encephalopathy associated with HIV and increased incidence of cognitive and behavioral impairments that are often observed in adults (Matida et al., 2009).

In Brazil, the classification of HIV infection (table 1) is based on clinical and immunological parameters, as proposed by the Centers for Disease Control and Prevention (CDC, 1994) and have been adapted to the brazilian reality (BRASIL, 2007). The immunological categories are based on the CD4 lymphocyte count, according to age and characterized from the immunological progress, such as: 1) absent, 2) and moderate 3) severe.

The clinical categories are based on clinical signs and symptoms (e.g. opportunistic infections). The clinical categories are: (N) asymptomatic; (A) mild symptoms; (B) moderate symptoms and (C) severe symptoms. In this definition, AIDS is the final stage of evolution associated with the presence of one or more opportunistic affections.

**Table 1 -** HIV infection classification (clinical and immunological) according to CDC

| | |
|---|---|
| **Immunological changes - Absent (1)** | |
| N1 | Absence of signs and/or clinical symptoms |
| A1 | Signs and/or mild clinical symptoms |
| B1 | Signs and/or moderate clinical symptoms |
| C1 | Signs and/or severe clinical symptoms |
| **Immunological changes - Moderate (2)** | |
| N2 | Absence of signs and/or clinical symptoms |
| A2 | Signs and/or mild clinical symptoms |
| B2 | Signs and/or moderate clinical symptoms |
| C2 | Signs and/or severe clinical symptoms |
| **Immunological changes - Severe (3)** | |
| N3 | Absence of signs and/or clinical symptoms |
| A3 | Signs and/or mild clinical symptoms |
| B3 | Signs and/or moderate clinical symptoms |
| C3 | Signs and/or severe clinical symptoms |

Neuropsychological impairments are related to the clinical progression of the infection, but they are subtle (Haase, Nicholas, Viana, Barreto & Pinto, 2014). The initial outcome of impairments seems to be associated with a pattern of mild cognitive impairments, especially in the areas of motor skills, processing speed and executive functions. The development of assessment protocols that population has been the subject of numerous studies in both children (Haase et al, 2014; Silva, 2011) and adults (Robertson, Liner & Heaton, 2009; Woods, Moore, Weber & Grant, 2009).

The impact of HAART in improving the living conditions of HIV infected people is undeniable, but the beneficial effects on neuropsychological functioning are not yet incontestable. Although several early studies have documented the effectiveness of antiretroviral drugs to improve or stabilize neurological deficits and neurodevelopment, particularly encephalopathy rates (Brouwers, Moss & Wolters, 1990), more recent studies

that examine the impact of ART on neurological development and neuroimaging findings have not demonstrated equally robust results (Jeremy, Kim, Nozyce, Nachman, McIntosh, Pelton, et al., 2005; Lindsey, Malee, Brouwers & Hughes, 2007; McCoig, Castrejon, Castaño, of Suman, Baez, Redondo et al, 2002; Thomaidis Bertou, Critselis, Spoulou, Kafetzis & Theodoridou, 2010). In a large scale study of neurocognitive function in younger with HIV after initiation of HAART, Jeremy et al. (2005) found significant impairment (> 1 standard deviation) in all areas of neurodevelopment for youngsters up to 17 years old including cognition, short-term memory, vocabulary and fine motor skills.

However, other studies have documented some improvements in neurocognitive performance and other parameters of the disease after initiation of HAART despite incomplete evidence of enhancements (Koekkoek, de Sonneville, Wolfs, Licht & Geelen, 2008; Shanbhag, Rutstein, Zaoutis, Zhao, Chao & Radcliffe, 2005; Tamula, Wolters, Walsek, Zeichner & Civitello, 2003). These results suggest that the suppression of viral load in the central nervous system and preservation of immunologic function is beneficial for neurocognitive function. Several studies in adults and children suggest that the deficits occurring prior to the use of HAART may be residual, and markers of disease such as viral load and CD4 are important predictors of subsequent neuropsychological results (Ellis, Badiee, Vaida, Letendre, Heaton, Clifford et al, 2011;. Jeremy et al, 2005; Nachman et al, 2012; Shanbhag et al, 2005; Smith, Chernoff, Williams, Malee, Sirois, Kammerer et al., 2012).

The cognitive model that best fits the profile of impairments in neuropsychology of HIV is a multicomponent model of executive functions (Diamond, 2013) which includes working memory, cognitive flexibility, inhibitory control, attention and problem solving.

Thus, executive functions has direct relations with working memory, cognitive flexibility and inhibitory control. The impairment of executive functions, memory and speed processing been well documented in neuropsychology of AIDS literature (Wachesler-Felder e Golden, 2002; Pearson, McGarth, Nozyce, Nichols, Raskino, Browers, Lifschitz, Baker & Englund; 2000). Neuropsychologically, cortico-subcortical circuits involving the prefrontal cortex implement the executive functions. The working memory being related to the dorsolateral prefrontal cortex, while monitoring / error detection and pulse control are related, respectively, to the prefrontal cortex dorsomedial and ventromedial (Fuster, 2008).

The presence of these impairments indicate the need for a battery of neuropsychological tasks that is able to discriminate the cognitive impairments of that specific population and contribute significantly to their clinical treatment (Akshoomoff et al., 2014).

From the social point of view, identifying neuropsychological markers that show early onset of cognitive impairments in children and teenagers with HIV can allow the implementation of specific educational measures to the maintenance of cognitive and social performance over time, thus resulting in the improvement quality of life and reduction of psychosocial impacts of cognitive damage caused by the infection. The impairments further observed in vertically infected populations were related to school performance and difficulties in social relations, both linked to the loss of executive functions commonly seen in HIV infection (Laughton, Cornell, Boivin & Van Rie, 2013; Garvie, Zeldow, Malee, Nichols, Smith, Williams & Wilkins, 2014; Melgarejo, Pino & Bassi, 2015).

Nevertheless, the studies related to children and adolescents should receive special

attention since in this age group the main characteristics of adult are form. Recent studies show that HAART does not cause significant improvements in cognition, but prevents its decline as the impaired immune system happens (Al-Khindi, Zakzanis and van Gorp, 2011). Thus, identification and intervention in developmental stages in childhood or adolescence may ensure maintenance of cognitive performance in this population near normal levels for longer.

After the implementation of the HAART, the focus of studies related neuropsychology of HIV is being focused on five aspects (Dawes and Grant, 2007):

1) Find neurocognitive deficits directly linked to HIV;

2) Determine whether the deficit is associated with comorbid conditions (e.g. psychiatric illness, nutritional deficiencies, drug use, hepatitis C, side effects of treatment);

3) Explore the relationship between neurocognitive deficit and disease variables (CD4 count, HIV biomarkers and neuroimaging);

4) Explore the relationship between neurocognitive impairment and activities of daily living in different cultures;

5) Determine the implications for the treatment, including antiretroviral schemes and adherence.

The objective of this dissertation was to investigate neuropsychological and behavioral characteristics in vertically HIV-infected children and adolescents. The hypotheses to be tested are:

1. There is a neuropsychological performance difference between groups (controls, HIV and AIDS);

2. The worsening of clinical and immunological parameters of infection are associated

with poorer neuropsychological performance;

3. The results on neuropsychological tasks of executive function, working memory and information processing speed will have greater ability to discriminate the groups;

4. Changes in neuropsychological functioning are associated with behavioral changes.

To this end, a literature review was conducted in order to identify the neuropsychological characteristics (Study I). After the first study, the results are presented with the data of neuropsychological instruments (Study II) and behavioral assessment (Study III).

**References**

Akshoomoff, N., Newman, E., Thompson, W. K., McCabe, C., Bloss, C. S., Chang, L., … for the Pediatric Imaging, Neurocognition, and Genetics Study. (2014). The NIH Toolbox Cognition Battery: Results from a Large Normative Developmental Sample (PING). *Neuropsychology*, *28*(1), 1–10. http://doi.org/10.1037/neu0000001

Al-Kindi, T.; Zakzanis, K., K. & van Gorp, G. (2011). Does antiretroviral therapy improve HIV associated cognitive impairment? A quantitative review of the literature. *Journal of the International Neuropsychological Society, 17*, 956-969.

Aylward, E.H., Henderer, J.D., McArthur, J.C., Brettschneider, P.D., Harris, G.J., Barta, P.E., & Pearlson, G.D. (1993). Reduced basal ganglia volume in HIV-1-associated dementia: Results from quantitative neuroimaging. *Neurology, 43*, 2099–2104.

Baldeweg, T., Catalan, J., Lovett, E., Gruzelier, J., Riccio, M., & Hawkins, D. (1995). Long-term zidovudine reduces neurocognitive deficits in HIV-1 infection. *AIDS, 9*, 589–596.

Brasil. Ministério da saúde. *Guia de tratamento clínico da infecção pelo HIV em pediatria*. Secretaria de Vigilância em Saúde, Programa Nacional de DST e Aids. – 3a Ed. – Brasília: Ministério da Saúde, 2007.

Brouwers, P., Moss, H., Wolters, P. (1990). Effect of continuous-infusion zidovudine therapy on neurpsychologic functioning in children with symptomatic human immunodeficiency vírus infection. *Journal of Pediatrics, 117*(6), 980-985.

Centers for Disease Control and Prevention. (1994). 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbidity and Mortality Weekly Reports, 43*, 1–10.

Centers for Disease Control and Prevention (2006). Reduction in perinatal transmission

of HIV infection— United States, 1985–2005. *MMWR, 55*, 592–97.

Centers for Disease Control and Prevention. (1994). 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbidity and Mortality Weekly Reports, 43*, 1–10.

Chen, Y., An, H., Zhu, H., Stone, T., Smith, J.K., Hall, C., Lin, W. (2009). White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV1 patients. *Neuroimage, 47*, 1154–1162.

Cohen, R.A., Boland, R., Paul, R., Tashima, K.T., Schoenbaum, E.E., Celentano, D.D., y Carpenter, C.C. (2001). Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. *AIDS, 15*, 341–345.

Dawes S, Grant I. (2007). Neurocognitive assessment of persons with HIV disease. *Handbook of Clinical Neurology. Edited By P.J. Vinken And G.W. Bruyn, 85*, 93-121.

Diamond, A. (2013). Executive Functions. *Annual Reviews of Psychology, 64*, 135-168.

Ellis, R.J., Badiee, J., Vaida, F., Letendre, S., Heaton, R.K., Clifford, D., et al. for the CHARTER Group. (2011). CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS, 10*(25), 1747-1751.

Fuster, J. (2008). *The prefrontal cortex* (4th. Edition). San Diego: Academic.

Garvie PA, Zeldow B, Malee K, Nichols SL, Smith RA, Wilkins ML, Williams PL. (2014). Discordance of Cognitive and Academic Achievement Outcomes in Youth With Perinatal HIV Exposure. *Pediatr Infect Dis J. Sep; 33*(9):e232-8.

Haase, V. G.; Nicolau, N. C.; Viana, V.N.; Barreto, G.V. & Pinto, J.A.(2014.). Executive function and processing speed in Brazilian HIV-infected children and adolescents. *Dementia & Neuropsychologia, 8*(1).

Hazra, R., Siberry, G. K., & Mofenson, L. M. (2010). Growing up with HIV: Children, adolescents, and young adults with perinatally Acquired HIV infection. *Annual Review of Medicine, 61*, 169-185.

Jeremy, R.J., Kim, S., Nozyce, M., Nachman, S., McIntosh, K., Pelton, S.I., et al. (2005). Neuropsychological functioning and viral load in stable antiretroviral therapy-experienced HIV infected children. *Pediatrics, 115*, 2, 380-387.

Kakehasi, F.M., Pinto, J. A., Romanelli, R., Carneiro, M., Cardoso, C. S., Tavares, M. C, Melo, V. H, Aguiar, R. A. (2008). Determinants and trends in perinatal human immunodeficiency virus type 1 (HIV-1) transmission in the metropolitan area of Belo Horizonte, Brazil: 1998 - 2005. *Memórias do Instituto Oswaldo Cruz, 103*, 351-377.

Koekkoek, S., de Sonneville, L. M. J., Wolfs, T. F. W., Licht, R. & Geelen, S. P. M. (2008). Neurocognitive function profile in HIV-infected school-age children. *European Journal of Pediatric Neurology*, 12, 290-297.

Laughton, B., Cornell, M., Boivin, M., & Van Rie, A. (2013). Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *Journal of The International AIDS Society, 16*(1). doi:10.7448/ias.16.1.18603

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-e693.

Matida, L. H., Ramos, A. N. Jr, Heukelbach, J, Hearst, N. & Brazilian Study Group on Survival of Children with AIDS (2009). Continuing improvement in survival for children with acquired immunodeficiency syndrome in Brazil. *Pediatric Infectious Diseases Journal*, 28, 920-922.

McCoig, C., Castrejón, M.M., Castaño, E., de Suman, O., Bãez, C., Redondo, W., et al. (2002). Effect of combination antiretroviral therapy on cerebrospinal fluid HIV RNA, HIV resistance, and clinical manifestations of encephalopathy. *Journal of Pediatrics, 141*, 36-44.

Melgarejo, M. , Pino, J. & Bassi, N. (2015). The Relationship between the Diagnosis of Human Immunodeficiency Virus (HIV) and Executive Functions in School Age Children. *Psychology, 6,* 600-605.

Nachman, S. A., Chernoff, M., Gona, P., Van Dyke, R. B., Dankner, W. M., Seage, G. R. 3rd, Oleske, J., Williams, P. L., & PACTG 219C Team (2009). Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Archives of Pediatric and Adolescent Medicine, 163*, 164-171.

Pearson, D. A., McGrath, N. M., Nozyce, M., Nichols, S. L., Raskino, C., Brouwers, P., Lifschitz, M. C., Baker, C. J. and Englund, J. A. (2000). Predicting HIV disease progression in children using measures of neuropsychological and neurological functioning. Pediatric AIDS clinical trials 152 study team . *Pediatrics; 106* (6).

Reger, M. Welsh, R., Razan, J., Martin, D. J., & Boone, K. B. (2002). A meta-analysis of the neuropsychological sequel of HIV infection. *Journal of the International Neuropsychological Society, 8*, 410-424.

Robertson, K.; Liner, J.; Heaton, R. (2009) Neuropsychological assessment of HIV-infected populations in international settings. *Neuropsychology Review*; 19:232-249.

Robertson, K.R., Robertson, W.T., Ford, S., Watson, D., Fiscus, S., Harp, A.G., & Hall, C.D. (2004). Highly active antirretroviral therapy improves neurocognitive functioning. *Journal of Acquired Immune Deficiency Syndromes, 36*, 562–566.

Shanbhag, M.C., Rutstein, R.M., Zaoutis, T., Zhao, H., Chao, D, & Radcliffe, J. (2005).

Neurocognitive functioning in pediatric human immunodeficiency virus infection: effects of combined therapy. *Archives of Pediatric and Adolescent Medicine, 159*(7), 651-656.

Silva, P. A. (2011). Habilidades matemáticas e memória operacional em crianças de 7 a 12 anos infectadas pelo HIV por transmissão vertical, em estado assintomático. Dissertação de mestrado apresentado ao curso de mestrado em Psicologia da Faculdade de Ciências e Letras de Assis da Universidade Estadual Paulista, Assis.

Smith, R., Chernoff, M., Williams, P.L., Malee, K.M., Sirois, P.A., Kammerer, B. et al. (2012). Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *The Pediatric Infectious Disease Journal, 31*, 592–598.

Suarez, S., Baril, L., Stankoff, B., Khellaf,M., Dubois, B., Lubetzki, C., y Hauw, J. (2001). Outcome of patients with HIV-1-related cognitive impairment on highly active antiretroviral therapy. *AIDS, 15*, 195–200.

Tamula, M.A.T., Wolters, P.L., Walsek, C., Zeichner, S., & Civitello, L. (2003). Cognitive decline with immunologic and virologic stability in four children with human immunodeficiency vírus disease. *Pediatrics,112*, 679-684.

Thomaidis, L., Bertou, G., Critselis, E., Spoulou, V., Kafetzis, D.A., & Theodoridou, M. (2010). Cognitive and psychosocial development of HIV pediatric patients receiving highly active antirretroviral therapy: a case-control study. *BMC Pediatrics*, *10*(99), 1-9.

Thompson, P.M., Dutton, R.A., Hayashi, K.M., Toga, A.W., Lopez, O.L., Aizenstein, H.J., & Becker, J.T. (2005). Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD41 T lymphocyte decline. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 15647–15652.

Tozzi, V., Balestra, P., Bellagamba, R., Corpolongo, A., Salvatori, M.F., Visco-Comandini, U.,Narciso, P. (2007). Persistence of neuropsychologic deficits despite long-

term highly active antirretroviral therapy in patients with HIV-related neurocognitive impairment: Prevalence and risk factors. *Journal of Acquired Immune Deficiency Syndromes, 45*, 174–182.

Wachsler-Felder, J. L. and Golden, C. J. (2002). Neuropsychological consequences of HIV in children: a review of current literature. *Clin Psychol Ver. 22*(3) 443-64.

Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive Neuropsychology of HIV-Associated Neurocognitive Disorders.*Neuropsychology Review*, *19*(2), 152–168. http://doi.org/10.1007/s11065-009-9102-5

Chapter 2 - **Neuropsychology in children with HIV: a integrative review***

**Gustavo de Val Barreto,[1, 2, 4] Virginia Nunes Viana,[1, 2] Jorge Andrade Pinto,[3] & Vitor Geraldi Haase[1, 2]**

1 - Developmental Neuropsychology Laboratory, Department of Psychology, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

2 - Programa de Pos-graduacao em Neurociencias, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

3 - Departamento de Pediatria, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

4 - Centro Universitário UNA, Minas Gerais, Brazil

Correspondig author at: Avenida Cristovão Colombo, 519, sala 804. Belo Horizonte, Brazil. Postal code: 30140-140. Gustavo de Val Barreto. E-mail: gvbarreto@gmail.com phone number 55 (31) 98829-6901.[1]

* The present paper was normalized according to the instructions for publication in the Brazilian Journal of Infectious Disease (https://www.elsevier.com/journals/brazilian-journal-of-infectious-diseases/1413-8670/guide-for-authors#68000).

**Neuropsychology in children with HIV: a integrative review**

**Abstract:** Neuropsychological data on children who are infected with human immunodeficiency virus (HIV) and the neurocognitive/neurodevelopmental effects of HIV infection are currently of great interest. The present review discusses the neuropsychological effects of HIV infection in childhood, including both vertical transmission and other forms of HIV infection, and neuropsychological outcomes. Different methodologies for neuropsychological assessment are used in the most of the studies, making comparisons between studies a difficult task. A literature search was performed in the PubMed, Medline, and Virtual Health Library databases using the following search terms: HIV, acquired immune deficiency syndrome (AIDS), neuropsychology, neurodevelopment, neurodevelopmental, and neurocognitive. A total of 42 articles were included in the present analysis between 2000 and May 2015 from a total of 1198 articles that were identified by the keywords. Articles were included in the present review if the study used any neuropsychological or neurodevelopmental measure. **Results**: The most frequency study design that was used was a cross-sectional design (*n* = 33 [78.57%]). The results showed HIV infection in children is a risk factor for developmental and neurodevelopmental delays, especially for children with high viral load, low $CD4^+$ counts, and more advanced stages of the disease. The most common neuropsychological deficits were a loss of general intelligence (subtle deficits), associated with decreases in processing speed, fine motor skills, executive function, working memory and attention. Compared with people without HIV, the average performance was lower for all of the neuropsychological skills that were evaluated in the analyzed studies.

**Keywords:** HIV; AIDS; neuropsychology; cognition; children; adolescent; young adults

## Introduction

Human immunodeficiency virus (HIV) infection has been increasingly common in young people around the world. In December 2014, the HIV/acquired immune deficiency syndrome (AIDS) program of the World Health Organization (WHO) estimated that approximately 33.2-36.9 million people live with HIV worldwide [1], approximately 3.4 million of whom are younger than 25 years old.

In neuropsychological terms, adolescence spans the age range of 10-25 years[2], a time period during which broad changes in childhood (0-9 years) and adolescence occur. The adoption of antiretroviral therapy (ART) for HIV infection in 1995 led to a dramatic decrease in mortality rates and consequent improvements in quality of life, subjective well-being, and daily functioning in people who are infected with HIV.

The development and popularization of ART were important factors in the epidemiological transition of HIV studies. ART has markedly reduced mortality rates and disease progression, but the contribution of such therapy to the reduction of cognitive impairments is not yet clear. Most studies have reported positive effects of ART on cognitive function [3-7], but some studies have not found significant effects [8], and others show only moderate effects on cognitive performance [9].

Generally, children who experience more rapid evolution of HIV infection can be categorized into two groups. Approximately one-third of children belong to the high-growth group, in which the onset of symptoms in the early months of life is usually associated with a sharp reduction of $CD4^+$ counts. In this group, infection likely occurred *in utero*. The other group, which comprises most HIV-infected children, follows an intermediate evolution, becoming symptomatic early in life [4]. As the number of new cases of vertical transmission are reduced and children and adolescents survive longer and reach adulthood, the focus of treatment has been on treatment adherence, drug

resistance, quality of life, and morbidity associated with the disease, such as cognitive and behavioral disorders [5]. Neuropsychologically, the most important transition is related to a decrease in the incidence of encephalopathy associated with HIV and the increased incidence of cognitive and behavioral impairments that are often observed in adults [6].

Cognitive disorders in children who are vertically infected with HIV have been recognized since the epidemic began. However, little information is available on the most specific forms of neuropsychological disorders in children and adolescents with HIV. Some neuropsychological studies that have been published in the post-ART era have employed cross-sectional designs and various cognitive measures that cover different areas of performance [10-12]. Losses of visuospatial skills and motor skills in children are often observed in such diseases as congenital hydrocephalus, in which damage occurs in subcortical white matter [13]. Substantial heterogeneity has been found in the ages of the study participants and the measures that are utilized. Most studies have focused on 6- to 16-year-old children, and other studies have focused on younger children (0-36 months of age). Given the variety of ages, neuropsychological measures, ART experience, and disease severity, we sought to review the literature on the neuropsychological characteristics of children and adolescents (0-24 years of age) who are infected with HIV.

Assessing neuropsychological or neurodevelopmental outcomes in children with HIV is a complex task because of potential confounding factors (e.g., illiteracy, malnutrition, and maternal substance abuse) especially in developmental countries. To evaluate different variables that may affect the development of people with HIV is extremely important to identify key aspects for the early identification of possible limitations and improving quality of life.

## Methods

The purpose of the present review was to answer the following question: which neuropsychological impairments are found in children, adolescents, and young adults (up to 24 years old) who are infected with HIV? According to Whitemore and Knafl (2005) [14], "integrative term has its origin in the integration of opinions, concepts or ideas from the surveys used in the method," showing the potential to build science. An integrative review is a specific review methodology that summarizes past empirical or theoretical works to provide a more comprehensive understanding of a particular phenomenon or healthcare problem.

A search for articles in PubMed, Medline and Virtual Health Library database that were published from 2000 to May 2015. There are considered articles that were published in english, spanish or portuguese language with the following keywords: 'HIV', 'AIDS', 'human immunodeficiency virus', 'neuropsychology', 'neurodevelopment', 'neurodevelopmental' and 'neurocognitive'. This search yielded 1198 articles, of which 248 were review articles and excluded. Inclusion and exclusion criteria (described below) were applied to the remaining articles (figure 1).

Empirical studies were selected that met the following inclusion criteria: (1) neuropsychological assessment measures and/or cognitive development measures were used, and (2) the study population consisted of participants aged ≤ 24 years. The exclusion criteria were the following: (1) review articles, (2) articles that did not use neuropsychological measures in the protocols, (3) articles that evaluated adults or the elderly population, (4) laboratory studies (e.g., that analyzed $CD4^+$ cell counts, test drugs, prevalence, or serum biomarkers in the absence of neuropsychological measures).

During article selection, the path of transmission by which the subjects contracted HIV infection were not consider. The final selected articles ($n = 42$) are presented in Table

1 according to the date of publication, with the sample size, neuropsychological constructs that were evaluated and main findings.

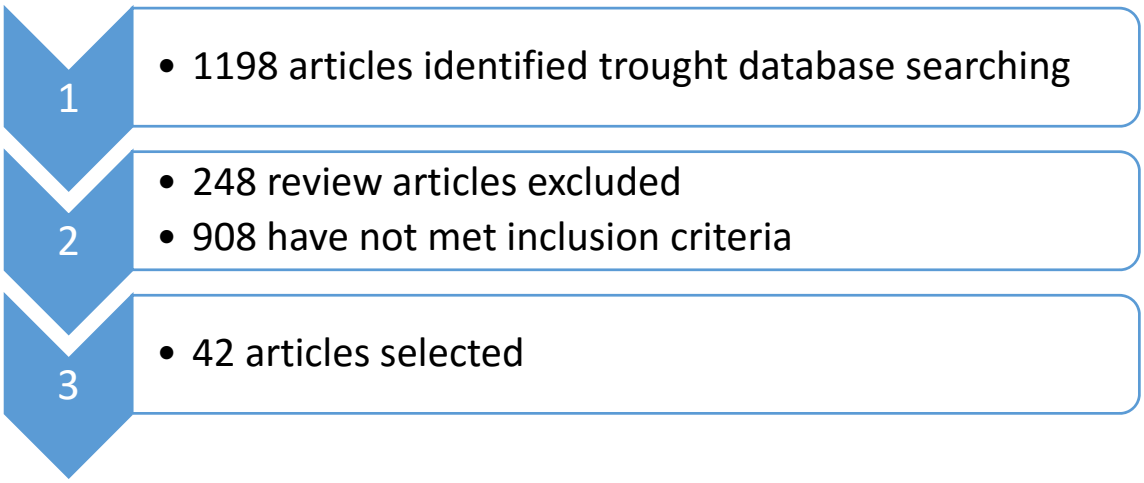



**Figure 1** – Literature search flow

**Results**

The search process yielded 42 articles meeting the inclusion criteria. The most common neuropsychological construct in the 42 articles analyzed herein was intelligence. Twenty-three studies used measures of intelligence to investigate neuropsychological characteristics. The diversity of repeated measurements makes it difficult to compare performance between studies. The measures ranged from general non-verbal intelligence (e.g., measured by Raven's Progressive Matrices) to more comprehensive measures (e.g., Wechsler's scale). Memory, motor skills, processing speed, attention, executive function, and neurodevelopment seem to be the most notable constructs that are evaluated in the neuropsychology of HIV infection.

With regard to study designs, the most prevalent was the cross-sectional design (33 studies [78.57%]). Five studies (11.90%) used a prospective design, and only four (9.52%) used a longitudinal design.

The presence of control groups was also a feature in 15 studies (35.60%). Sixteen studies used only the national standards of the instruments. Three studies established relationships between viral load and neuropsychological performance in the absence of a control group. Six studies compared the effects of ART on neuropsychological performance. One study evaluated neuropsychological rehabilitation, and one study compared groups with different subtypes of the virus.

Table 1. Summary of recent neuropsychological studies in HIV-infected children.

| | **Article** | **Authors** | **Year** | **Sample (*n*)** | **Age** | **Study design** | **Neuropsychological constructs evaluated** | **Main results** |
|---|---|---|---|---|---|---|---|---|
| 1. | 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. | Kandawasvika et al. [15] | 2015 | 306<br>32 HIV-infected<br>121 exposed uninfected<br>153 unexposed uninfected | 6-8 years | Cross-sectional | Neurodevelopment scales | Deficits in perceptual performance in HIV-infected group.<br>49 children had cognitive impairment with no difference in general cognitive function |
| 2. | Poorer Cognitive Performance in Perinatally HIV-Infected Children Versus Healthy Socioeconomically Matched Controls | Cohen et al. [16] | 2015 | 35 perinatally HIV-infected children + 37 healthy | 8-18 years | Cross-sectional | Intelligence, information processing speed, attention, memory, executive function, and visual-motor function | Cognitive performance in HIV-infected children was poor compared with Socio Economic Status matched healthy controls |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3. | Early Viral Suppression Improves Neurocognitive Outcomes in HIV-infected Children | Crowell et al. [17] | 2015 | 410 | 7-16 years | Prospective cohort | Intelligence | Early viral suppression was associated with a positive impact on cognitive functioning during childhood |
| 4. | Executive function and attention-deficit/hyperactivity disorder in Ugandan children with perinatal HIV exposure | Burkey et al. [18] | 2015 | 232 | 3-12 years | Cross-sectional | Executive function, attention, general cognitive ability | Significant executive dysfunction |
| 5. | Executive functions and attention in Colombian children with human immunodeficiency virus infection | Guevara Ramos et al. [19] | 2014 | 30 | 6-16 years | Cross-sectional | Attention, verbal fluency, memory | The alterations were found in cognitive flexibility, selective attention, conceptual skills, planning and organization, and impaired psychomotor speed. |
| 6. | Executive function and processing | Haase et al. [20] | 2014 | 41 + 82 control | 5-17 | Cross-sectional | Executive functions, | Motor and cognitive |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | speed in Brazilian HIV-infected children and adolescents | | | group | years | | processing speed, attention, intelligence, motor skills | processing speed and executive function appeared to be the most discriminative domains. |
| 7. | An analysis of select emerging executive skills in perinatally HIV-1-infected children | Llorente et al. [21] | 2014 | 161 HIV-positive ($n$ = 76) and HIV-negative ($n$ = 85) | 8-12 years | Cross-sectional | Executive functions | The apparent deficit in executive function in HIV-positive children was found to be largely attributable to differential psychosocial and environmental factors. |
| 8. | Discordance of cognitive and academic achievement outcomes in youth with perinatal HIV exposure | Garvie et al. [22] | 2014 | 295 perinatally HIV-infected children + 167 controls | 7-16 years | Cross-sectional | Intelligence | Both groups scored about 1 standard deviation of intellectual functioning across domains (). |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 9. | Cognitive deficits in HIV infected children | Ravindran et al. [23] | 2014 | 20 clinical group + 20 control group | 8-12 years | Cross-sectional | Attention, language, visual memory, verbal learning and memory, visuoperceptual functions, visuospatial functions, visuomotor functions, fine motor performance, and executive functions | HIV-infected children showed substantial impairments in the domains of attention, language, verbal learning and memory, visuomotor functions, fine motor performance, and executive functions. |
| 10. | Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV | Kerr et al. [24] | 2014 | 167 clinical group + 167 control group | | Cross-sectional | Intelligence, motor skills, behavior | Lower scores in verbal IQ, full scale IQ, and memory. |
| 11. | Neurocognitive function in HIV-positive children in a developing country | Walker et al. [25] | 2013 | 15 clinical group + 15 control group | 7-10 years | Cross-sectional | Intelligence, short-term memory, selective attention, fine motor skills | Lower scores in memory, attention, and motor coordination. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 12. | Neurocognitive functioning in antiretroviral therapy-naïve youth with behaviorally acquired human immunodeficiency virus | Nichols et al. [26] | 2013 | 220 | 18-24 years | Cross-sectional | Memory, motor skills, attention, executive function, and reading ability | Deficits in episodic memory and fine-motor skills emerging as the most commonly affected ability areas. |
| 13. | Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection | Foster et al. [27] | 2012 | 38 clinical group + 35 control group | 8-17 years | Cross-sectional | Verbal memory, processing speed, motor speed, vigilance and sustained attention, executive function, and behavioral assessment | 1 SD below average in all constructs. |
| 14. | A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve “slow progressors” | Hoare et al[28] . | 2012 | 12 + 12 control group | 8-12 years | Cross-sectional | Intelligence, visuospatial processing, visual memory, and executive function | Performed significantly worse than controls on all of the measures used. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 15. | Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4 cell counts. | Ruel et al. [29] | 2012 | 93 clinical group + 106 control group | 6-12 years | Cross-sectional | Attention, neurodevelopment, and motor skills | Significant motor and cognitive deficits. |
| 16. | Neurodevelopmental delay among HIV-infected preschool children receiving antiretroviral therapy and healthy preschool children in Soweto, South Africa | Lowick et al. [30] | 2012 | 30 + 30 control group | 5-6 years | Cross-sectional | Neurodevelopment scales | Severe deficits in the HIV-infected group. |
| 17. | Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth | Nachman et al. [31] | 2012 | 319 | 6-17 years | Prospective observational | Working memory and processing speed | Worse performance on IQ scores, memory, and processing speed. |
| 18. | Neuropsychological function and cerebral metabolites in HIV-infected youth | Nagarajan et al. [32] | 2012 | 30 (16 clinical group + 15 vertical transmission) + | 13-25 years | Cross-sectional | Attention/processing speed, psychomotor ability, and executive function | Poorer attention and processing speed. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 14 control group | | | | |
| 19. | Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence | Smith et al. [33] | 2012 | 558 (88 HIV class C + 270 HIV no C) + 200 exposed uninfected | 7-16 years | Cross-sectional | Intelligence and behavior | Lower cognitive performance in HIV class C. |
| 20. | Neuropsychological evaluation, psychosocial factors, and psychiatric comorbidity of children with HIV infection | Castro et al. [34] | 2011 | 23 clinical group | 3-17 years | Cross-sectional | Motor skills, intelligence, memory, attention | Lower cognitive performance on IQ tests (-1 SD) and deficits in memory and attention. |
| 21. | HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children | Boivin et al. [35] | 2010 | 102 clinical group | 6-12 years | Cross-sectional | Neurodevelopment scales | Children with type A performed more poorly than those with type D on all measures. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 22. | Poor cognitive functioning of school-aged children in Thailand with perinatally acquired HIV infection taking antiretroviral therapy. | Puthanakit et al. [36] | 2010 | 121 (39 HIV-infected + 40 HIV-affected) + 42 control children | 6-12 years | Prospective cohort study | Intelligence | Lower performance on intelligence tests. Cognitive function did not improve after ART. |
| 23. | A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV | Boivin et al. [37] | 2010 | 60 (perinatal infection; 23 on ART) | 6-16 years | Cross-sectional | Learning, psychomotor speed, working memory, and attention | Improved learning and attention. |
| 24. | Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study | Thomaidis et al. [38] | 2010 | 20 vertically infected children + 20 controls | 3-18 years | Cross-sectional | Intelligence | HIV patients without neuroimaging abnormalities had similar cognitive development as their healthy peers. |
| 25. | Relationships between markers of vascular dysfunction and | Kapetanovic et al. [39] | 2010 | 89 | 7-16 years | Cross-sectional | Intelligence | Decreases were significant in the verbal |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | neurodevelopmental outcomes in perinatally HIV-infected youth | | | | | | | comprehension, perceptual reasoning, and Full-Scale IQ scores. |
| 26. | Effects of perinatal HIV infection and early institutional rearing on physical and cognitive development of children in Ukraine | Dobrova-Krol et al. [40] | 2010 | 64 | 34-74 months | Cross-sectional | Intelligence, Theory of Mind | Poor cognitive performance in HIV group. |
| 27. | Neurocognitive function profile in HIV-infected school-age children | Koekkoek et al. [12] | 2008 | 22 vertically infected children | 6-17 years | Cross-sectional | Intelligence, working memory, attention, information processing, executive function, and visuospatial perception | Executive function and processing speed emerged as the most sensitive cognitive measures in relation to HIV disease. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 28. | The extent of delay of language, motor, and cognitive development in HIV-positive infants | Baillieu et al. [41] | 2008 | 40 | 18-30 months | Cross-sectional | Neurodevelopment scales | Delay in cognitive and motor development. |
| 29. | Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa, Democratic Republic of the Congo | Van Rie et al. [42] | 2008 | 35 clinical group + 90 control children | 18-72 months | Cross-sectional | Neurodevelopment scales, motor skills, intelligence, language | Delay in cognitive function, motor skills, language expression, and language comprehension. |
| 30. | Immunologic, virologic, and neuropsychologic responses in human immunodeficiency virus-infected children receiving their first highly active antiretroviral therapy regimen | Hazra et al. [43] | 2007 | 12 | 4-18 years | Cross-sectional | Intelligence | Most children exhibited stable cognitive function over the course of the study. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 31. | Effects of perinatal HIV infection and associated risk factors on cognitive development among young children | Smith et al. [44] | 2006 | 117 | 3-7 years | Longitudinal | Neurodevelopment scales | Children with HIV infection and class C status scored significantly lower in all domains of cognitive development, across all time points. |
| 32. | A behavioral and cognitive profile of clinically stable HIV-infected children | Nozyce et al. [45] | 2006 | 274 | 2-17 years | Cross-sectional | Intelligence | 1 SD below population norms |
| 33. | Cognitive functioning in school-aged children with vertically acquired HIV infection being treated with highly active antiretroviral therapy (HAART) | Martin et al. [46] | 2006 | 41 | 6-16 years | Cross-sectional | Intelligence | Children with minimal to moderate CT brain scan abnormalities scored significantly lower than children with normal scans. Children with worse immune status ($CD4^+$ |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | counts ≤ 500) scored lower on subtests that measured processing speed. |
| 34. | Effects of highly active antiretroviral therapy (HAART) on psychomotor performance in children with HIV disease | Koekkoek et al. [47] | 2006 | 34 (16 never on ART, 7 untreated, 11 on HAART more than 1 year) | 4-12 years | Longitudinal | Motor skills | At the 12-month evaluation, psychomotor performance had deteriorated substantially on all tasks in both the newly treated and untreated children. |
| 35. | Neuropsychological functioning and viral load in stable antiretroviral therapy-experienced HIV-infected children | Jeremy et al. [48] | 2005 | 489 | 4 months - 17 years | Prospectively for 48 weeks | Behavior and motor skills | At week 48, even children with a viral load response below the level of detection still showed poorer |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | neuropsychological functioning compared with established norms. |
| 36. | Neurocognitive functioning in pediatric human immunodeficiency virus infection: effects of combined therapy | Shanbhag et al. [49] | 2005 | 146 vertically infected | Group 1 (2-14 years) Group 2 (8-22 years) | Retrospective cohort study | Intelligence | Neurocognitive scores remained stable over time. |
| 37. | Early neurodevelopmental markers predictive of mortality in infants infected with HIV-1. | Llorente et al. [50] | 2003 | 157 | 3-6 years | Longitudinal | Neurodevelopment scales | Low cognitive and psychomotor developmental scores at 4 months of age were significant predictors of early mortality in infants infected perinatally with HIV. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 38. | Genetic influence of CCR5, CCR2, and SDF1 variants on human immunodeficiency virus 1 (HIV-1)-related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. | Singh et al. [51] | 2003 | 1049 | 42 days - 15 years | Longitudinal | Neurodevelopment scales, intelligence | Lower average scores. |
| 39. | Cognitive decline with immunologic and virologic stability in four children with human immunodeficiency virus disease | Tamula et al. [52] | 2003 | 4 vertically acquired HIV | | Cross-sectional | Intelligence | Two of the four showed improved or stable functioning, indicated by the results of follow-up psychometric testing. |
| 40. | Cognitive development in school-age children with vertically transmitted HIV infection. | Blanchette et al. [53] | 2002 | 14 (2 asymptomatic, 8 mildly symptomatic, and 4 with AIDS) + 11 | 6-14 years | Cross-sectional | Intelligence, language, academic measures, memory, attention, motor speed, and coordination | No significant differences in academic measures, lower performance on measures of fine motor skills and motor |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | sibling controls | | | | strength. |
| 41. | Cognitive and motor development in children with vertically transmitted HIV infection | Blanchette et al. [54] | 2001 | 25 vertically acquired HIV + 25 children born to HIV-positive mothers but not infected with the virus | 6-37 months | Cross-sectional | Neurodevelopment and motor skills | HIV group scored lower on all measures. |
| 42. | Neuropsychological evaluation of neurologically asymptomatic HIV-infected children | Bisiacchi et al. [10] | 2000 | 42 | 6-15 years | Cross-sectional | Intelligence, language, executive function, memory, and visuospatial skills | Deficits in executive function. Memory and visuospatial abilities deficits only in AIDS children. |

**Intelligence**

intelligence can be defined as the ability to solve new problems and adapt to new situations, and there are some explanatory theories about its operation [59}. Intelligence was the most investigated construct in the studies analyzed herein (19 studies). The pattern of damage that was reported in the studies consisted of the lowering of intelligence performance. Such deficit was associated with clinical disease progression but generally remained approximately 1-1.5 standard deviations below average performance. Three studies [12,45,54] reported significant differences between groups. Studies that included control groups [2, 6, 8, 10, 11, 14, 22, 24, 29] and compared performance with the clinical group and used the available national standards found similar results.

Comparing average intelligence performance between groups may not be an appropriate way to represent the damage found, given the great heterogeneity of the groups of infected children and adolescents [20]. Losses of intelligence may represent subtle general cognitive deficits, and such deficits may mask specific losses that impair neuropsychological functioning in people with HIV. When intellectual performance was found to not be significantly impaired, other cognitive domains emerged as candidates of markers of cognitive impairments that are related to HIV infection. Losses in memory (specifically working memory), executive function, processing speed, attention, and fine motor skills were found even in the absence of losses of intelligence. These cognitive domains are related to intelligence and have shared components.

Nonetheless, comparisons of average performance between groups may still be a suitable way of representing the damage found, given the large heterogeneous groups of HIV-infected children and adolescents. Differents findings between studies may be partially attributable to the different measures used. General intelligence measures can mask more subtle impairments, particularly skills that are related to the functioning of prefrontal structures.

**Motor skills**

Impairments in motor skills, specifically fine motor skills, have been shown to be a good indicator of losses associated with HIV. Nineteen studies evaluated motor skills in their protocols [16, 19, 20, 23-27, 29, 32, 33, 37, 41, 43, 48, 49, 51, 53, 54]. The results showed that fine motor skills are generally compromised in groups with more advanced stages of the disease and appear to be compromised since the beginning of childhood development [16, 20, 27, 29, 34, 37]. Baillieu et al. [41] and Van Rie et al. [43] investigated children between 18 and 72 months of age who were vertically infected. These children already presented developmental delays related to motor skills compared with population norms.

**Executive function**

Executive function in children and adolescents with HIV are especially interesting because of its relationship with school performance, adherence to treatment, and behavior in general. They could be defined by the skill set that allows you to direct the behavior goals and solve short, medium and long term problems [20]. Of the 42 studies analyzed, 12 used measures of executive function and suggested that this domain is the most sensitive to discriminating the damage associated with HIV infection [10, 12, 16, 18-21, 23, 26-28, 32]. Haase et al. [20] evaluated a group of children and adolescents who were vertically infected with HIV, and the results in executive function and processing speed tasks were the most notable. Similarly, Koekkoek et al. [16] described losses of executive function and processing speed even when the group of subjects presented average performance in general intelligence tasks.

Processing speed deserves special attention in the literature on neuropsychological aspects

of HIV infection in children [12, 20]. In studies of neuropsychological performance in children, processing speed was one of the most vulnerable cognitive abilities, especially when the presence of viral load was controlled between participants (i.e., higher viral load is associated with deficits in processing speed) [20, 31, 33].

The relationship between processing speed and executive function can be explained by their interdependence. With higher processing speed, more information can be processed per unit time, and more processing power becomes available for executive function and working memory [57-59].

One of the possible consequences of executive function impairment in everyday life is the loss of academic performance. Although important, few studies have investigated losses of academic performance as a possible outcome of neuropsychological impairment in HIV-infected individuals. One of the first studies in the literature found no difference in performance in the experimental group compared with the control group. Low scores were found in reading, writing, and mathematics, although such scores were around the average, but shortcomings were found in corresponding measures of cognitive skills[55].

**Attention**

Attention was investigated in 14 studies [12,16,18-20, 23, 25-27, 29, 32, 34, 37, 54]. Measures of attention varied with the type of attention (sustained, alternating and concentrated) that was being measured, and these measures were associated with measures of executive function and memory. In the study by Boivin et al., [37] the intervention that was used (i.e., cognitive rehabilitation) improved performance in attention and learning tasks. Attentional impairment suggested that this cognitive ability is vulnerable to HIV infection.

**Language**

Language was investigated in three studies with children or adolescents with HIV. Language disorders are concerning in this population because of the influence of this ability on academic and social success. A few studies reported the subtle loss of language skills,[23, 43] but still unclear is the contribution of HIV infection to these language disorders.

**Visuospatial processing**

Visuospatial processing was assessed in four studies [10,12, 23, 28], using complex Rey figure and Corsi blocks. Children with HIV scored below the norms and control group in these studies. In the study by Bisiacchi et al.,[10] deficits were found only in children with AIDS. The use of different types of measurements complicates the comparison of the size of the damage effect. They are evident that the damage in visospatial processing are related impairments white matter [55].

**Neurodevelopmental scales**

The use of developmental scales was found in 10 studies [15, 29, 30, 36, 41, 42, 44, 50, 52, 54]. The developmental scales assessed different developmental characteristics and were generally used in younger populations. Children with HIV showed greater losses (motor and cognitive) on these scales compared with the standards. One study [37] compared performance in 6 to 12 year-old children with different subtypes of HIV (types A and D) and found that children with type A had significantly worse performance than children who were infected with type D.

The traditional markers of disease progression and severity ($CD4^+$, viral load and history of AIDS-defining illnesses [CDC class C]) are associated with poorer cognitive performance [21, 29, 33, 46].

One study [36] investigated the effectiveness of computerized neuropsychological rehabilitation in infected children, reporting a positive effect on learning and attention.

**Discussion**

The heterogeneity of neuropsychological impairments appears to be one of the main factors that hinder the discovery of a neuropsychological impairment profile associated with the presence of HIV [19, 20, 23]. HIV directly influences neuropsychological development, and such variables as socioeconomic status, access to medication, quality of life, opportunistic infections, and access to health conditions can influence the damage that is specifically caused by the presence of HIV in the body [12].

The articles analyzed herein showed that cognitive impairment that is associated with HIV infection is present throughout the development of HIV-infected individuals. Studies have shown that HIV-infected children underperformed the standards that were used in the studies. Studies that included a control group found lower performance in the clinical group. Comparisons of performance in subjects with HIV revealed another pattern, in which larger neuropsychological losses were associated with more severe levels of the disease. Specifically class C infection increased the probability of having lower neuropsychological performance [21, 32]. Two studies reported no loss of neuropsychological performance, but neither study used a control group and the samples were compared at two different time points [49,50].

The use of ART in children and adolescents can reduce the impact of cognitive impairments [17], and the initiate of ART in childhood may be beneficial for maintaining better neuropsychological performance [37]. Nonetheless, no consensus has been reached regarding the use of ART for improving cognitive abilities [8].

Small sample sizes can be problematic for generalizing the results as well as different

interference factors in the development of children infected, such conditions could be related to pregnancy (i.e., nutrition, drugs, and alcohol) and the environment where children develop may be confounding factors in the interpretation of the effects of solely the presence of HIV.

Because neuropsychological impairments are very heterogeneous, a model of assessment that includes a set of broader skills is necessary to identify subtle damage that can compromise this population. Models of neuropsychological assessment for the HIV-infected population must consider the following domains: intelligence, executive function, fine motor skills, processing speed, attention, and working memory. Still unclear are the factors that impact school performance and language ability and few studies have explored these variables.

**Conclusion**

Neuropsychological impairments associated with HIV infection have been widely studied, especially in the post-ART era, which has increased the survival of infected patients. Since the introduction of ART, research has focused on more subtle damage that is related to the presence of HIV and possible consequences of treatment and comorbidities [44, 54].

The neuropsychological assessment in children and young adults is a relatively new area of research after the introduction of ART, which changed the mode of progression of the disease. Thus, the focus of studies appears to be changing, more toward the identification of long-term damage that may be associated with infection and how such neuropsychological losses can affect performance in everyday life and impact quality of life. Another focus of the studies appears to be the effectiveness of ART in preventing cognitive decline.

Neuropsychological impairment associated with HIV infection was generally found in the studies analyzed herein. The extent and degree of impairment appear to be related to various conditions, ranging from the socioeconomic status of the studied population, access to healthcare

and education, and progression of the disease. Increase of $CD4^+$, decrease of viral load and CDC classification C are associated with poorer performance on neuropsychological measures. Studies that utilized a longitudinal design [44, 47, 50, 52] did not concluded whether the viral load or $CD4^+$ counts can singly explain worse performance. Having an AIDS-defining illness is strongly associated with cognitive impairment and specifically linked to the risk of encephalopathy.

Losses of general intelligence are more insidious compared with other deficits, and methods of assessment should determine the neuropsychological impairments in HIV infection that are associated with the following skills: executive function, fine motor skills, processing speed, attention, and working memory.

One of the biggest challenges in investigating the effects of HIV on neurodevelopment and neuropsychological functioning in children and adolescents with HIV is the complex interaction between biological and medical factors associated with HIV and the influence of social and environmental factors (access to healthcare and education, housing, and so on). Many studies attempt to control the contributions of these factors to performance by including control groups matched for age, sex and socioeconomic status to identify the variables that can be attributed solely to the presence of infection. Different methodological designs, various measures, the limited number of critical outcome variables and the wide range of treatments within the sample can make it difficult to compare results and generalize the findings. Despite the difficulties, much progress has been made in understanding vulnerability and neurocognitive development in children and adolescents who are infected with HIV. Future research should specifically investigate neuropsychological characteristics associated with ART, effects on cognition, and impacts on everyday functioning.

**Conflicts of interest**

The authors have no conflict of interest to declare.

**References**


1. Brasil, Ministério da Saúde. Boletim Epidemiológico - AIDS e DST. Brasília: Ministério da Saúde, Ano I, n.1. [até a semana epidemiológica 52ª - dezembro de 2013. 01ª à 52ª - semanas epidemiológicas - janeiro a dezembro de 2013] 2013.

2. American Psychological Association. Developing adolescents: a reference for professionals. Washington, DC: American Psychological Association, 2002.

3. Baldeweg, T, Catalan, J, Lovett, E, Gruzelier, J, Riccio, M, Hawkins, D. Long-term zidovudine reduces neurocognitive deficits in HIV-1 infection. AIDS, 1995, 9, 589-596.

4. Cohen, RA, Boland, R, Paul, R, Tashima, KT, Schoenbaum, EE, Celentano, DD, Schuman, P, Smith, DK, Carpenter, CC. Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. AIDS, 2001, 15, 341-345.

5. Robertson, KR, Robertson, WT, Ford, S, Watson, D, Fiscus, S, Harp, AG, Hall, CD Highly active antirretroviral therapy improves neurocognitive functioning. Journal of Acquired Immune Deficiency Syndromes, 2004 36, 562-566.

6. Suarez, S, Baril, L, Stankoff, B, Khellaf, M, Dubois, B, Lubetzki, C, Hauw, JJ. Outcome of patients with HIV-1-related cognitive impairment on highly active antiretroviral therapy. AIDS, 2001, 15, 195-200.

7. Tozzi, V, Balestra, P, Bellagamba, R, Corpolongo, A, Salvatori, MF, Visco-Comandini, U, Vlassi, C, Giulianelli, M, Galgani, S, Antinori, A, Narciso, P. Persistence of neuropsychologic deficits despite long-term highly active antirretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. Journal of Acquired Immune Deficiency Syndromes, 2007, 45, 174-182.

8. Al-Khindi, T, Zakzanis, KK, van Gorp, WG. Does antiretroviral therapy improve HIV associated cognitive impairment? A quantitative review of the literature. Journal of the International Neuropsychological Society, 2011, 17, 956-969.

9. Dawes, S, Grant, I. Neurocognitive assessment of persons with HIV disease. Handbook of Clinical Neurology, 2007, 85, 93-121.

10. Bisiacchi, PS, Suppiej, A, Laverda, A. Neuropsychological evalution of neurologically assymptomatic HIV-infected children. Brain and Cognition, 2000, 43, 49-52.

11. Blanchette, N, Smith, ML, King, S, Fernandes-Penney, A, Read, S. Cognitive development in school-age children with vertically transmitted HIV infection. Developmental Neuropsychology, 2002, 21(3), 223-241.

12. Koekkoek, S, de Sonneville, LMJ, Wolfs, TFW, Licht, R, Geelen, SPM. Neurocognitive function profile in HIV-infected school-age children. European Journal of Pediatric Neurology, 2008, 12, 290-297.

13. Hasan, KM, Eluvathingal, TJ, Kramer, LA, Ewing-Cobbs, L, Dennis, M, Fletcher, JM. White matter microstructural abnormalities in children with spina bifida myelomeningocele and hydrocephalus: a diffusion tensor tractography study of the association pathways. Journal of Magnetic Resonance Imaging, 2008, 27, 700-709.

14. Whittemore, R, Knafl, K. The integrative review: updated methodology. Journal of Advanced Nursing, 2005, 52(5), 546-553.

15. Kandawasvika, GQ, Kuona, P, Chandiwana, P, Masanganise, M, Gumbo, FZ, Mapingure, MP, Nathoo, K, Stray-Pedersen, B. 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 Neuropsychology, 2015, 21(1), 106-120.

16. Cohen, S, Ter Stege, JA, Geurtsen, GJ, Scherpbier, HJ, Kuijpers, TW, Reiss, P, Schmand, B, Pajkrt, D. Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. Clinical Infectious Diseases, 2015, 60(7), 1111-1119.

17. Crowell, CS, Huo, Y, Tassiopoulos, K, Malee, KM, Yogev, R, Hazra, R, Rutstein, RM, Nichols, SL, Smith, RA, Williams, PL, Oleske, J, Muller, WJ. Early viral suppression improves neurocognitive outcomes in HIV-infected children. AIDS, 2015, 29(3), 295-304.

18. Burkey, MD, Murray, SM, Bangirana, P, Familiar, I, Opoka, RO, Nakasujja, N, Boivin, M, Bass, JK. Executive function and attention-deficit/hyperactivity disorder in Ugandan children with perinatal HIV exposure. Global Mental Health, 2015, 2, e4 doi:10.1017/gmh.2015.2.

19. Guevara Ramos, JD, Rodriguez Gutierrez, T, Cabrera, SC, Izquierdo Bello, AH. Executive functions and attention in colombian children with human immunodeficiency virus infection. Acta Neurol Colomb, 2014, 30(4), 240-246.

20. Haase, VG, Nicolau, NC, Viana, VN, de Val Barreto, G, Pinto, JA (2014). Executive function and processing speed in Brazilian HIV-infected children and adolescents. Dementia and Neuropsychologia, 2014, 8(1), 32-39.

21. Llorente, AM, Brouwers, P, Leighty, R, Malee, K, Smith, R, Harris, L, Serchuck, LK, Blasini, I, Chase, C. An analysis of select emerging executive skills in perinatally HIV-1-infected children. Applied Neuropsychology: Child, 2014, 3(1), 10-25.

22. Garvie, PA, Zeldow, B, Malee, K, Nichols, SL, Smith, RA, Wilkins, ML, Williams, PL. Discordance of cognitive and academic achievement outcomes in youth with perinatal HIV exposure. Pediatric Infectious Disease Journal, 2014, 33(9), e232-e238.

23. Ravindran, OS, Rani, MP, Priya, G. Cognitive deficits in HIV infected children. Indian Journal of Psychological Medicine, 2014, 36(3), 255-259.

24. Kerr, SJ, Puthanakit, T, Vibol, U, Aurpibul, L, Vonthanak, S, Kosalaraksa, P, Kanjanavanit, S, Hansudewechakul, R, Wongsawat, J, Luesomboon, W, Ratanadilok, K, Prasitsuebsai, W, Pruksakaew, K, van der Lugt, J, Paul, R, Ananworanich, J, Valcour, V. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. AIDS Care, 2014, 26(11), 1327-1335.

25. Walker, SY, Pierre, RB, Christie, CD, Chang, SM. Neurocognitive function in HIV-positive children in a developing country. International Journal of Infectious Diseases, 2013, 17(10), e862-e867.

26. Nichols, SL, Bethel, J, Garvie, PA, Patton, DE, Thornton, S, Kapogiannis, BG, Ren, W, Major-Wilson, H, Puga, A, Woods, SP. Neurocognitive functioning in antiretroviral therapy-naïve youth with behaviorally acquired human immunodeficiency virus. Journal of Adolescent Health, 2013, 53(6), 763-771.

27. Foster, SB, Lu, M, Glaze, DG, Reuben, JM, Harris, LL, Cohen, EN, Lee, BN, Zhao, E, Paul, ME, Schwarzwald, H, McMullen-Jackson, C, Clark, C, Armstrong, FD, Brouwers, PY, Miller, TL, Colin, AA, Scott, GB, Shahzeidi, S, Willen, EJ, Asthana, D, Lipshultz, SE, Thompson, BW, Shearer, WT. Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. Clinical Immunology, 2012, 144(1), 13-23.

28. Hoare, J, Fouche, JP, Spottiswoode, B, Donald, K, Philipps, N, Bezuidenhout, H, Mulligan, C, Webster, V, Oduro, C, Schrieff, L, Paul, R, Zar, H, Thomas, K, Stein, D. A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve "slow progressors." Journal of Neurovirology, 2012, 18(3), 205-212.

29. Ruel, TD, Boivin, MJ, Boal, HE, Bangirana, P, Charlebois, E, Havlir, DV, Rosenthal, PJ, Dorsey, G, Achan, J, Akello, C, Kamya, MR, & Wong, JK. Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4 cell counts. Clinical Infectious Diseases, 2012, 54(7), 1001-1009.

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

31. Nachman, S, Chernoff, M, Williams, P, Hodge, J, Heston, J, Gadow, KD. Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth. Archives of Pediatrics and Adolescent Medicine, 2012, 166(6), 528-535.

32. Nagarajan, R, Sarma, MK, Thomas, MA, Chang, L, Natha, U, Wright, M, Hayes, J, Nielsen-Saines, K, Michalik, DE, Deville, J, Church, JA, Mason, K, Critton-Mastandrea, T, Nazarian, S, Jing, J, Keller, MA. Neuropsychological function and cerebral metabolites in HIV-infected youth. Journal of Neuroimmune Pharmacology, 2012, 7(4), 981-990.

33. Smith, R, Chernoff, M, Williams, PL, Malee, KM, Sirois, PA, Kammerer, B, Wilkins, M, Nichols, S, Mellins, C, Usitalo, A, Garvie, P, Rutstein, R. Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. Pediatric Infectious Disease Journal, 2012, 31(6), 592-598.

34. Castro, PM, Martínez, VY, González, NI, Velásquez, AJ, Castillo, IG, Sánchez, VL. [Neuropsychological assessment, psychosocial factors, and psychiatric comorbidity of children with HIV infection]. Revista Chilena de Infectologia, 2011, 28(3), 248-254.

35. Boivin, MJ, Ruel, TD, Boal, HE, Bangirana, P, Cao, H, Eller, LA, Charlebois, E, Havlir, DV, Kamya, MR, Achan, J, Akello, C, Wong, JK. HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children. AIDS, 2010, 24(8), 1163-1170.

36. Puthanakit, T, Aurpibul, L, Louthrenoo, O, Tapanya, P, Nadsasarn, R, Insee-ard, S, Sirisanthana, V. Poor cognitive functioning of school-aged children in Thailand with perinatally acquired HIV infection taking antiretroviral therapy. AIDS Patient Care and STDs, 2010, 24(3), 141-146.

37. Boivin, MJ, Busman, RA, Parikh, SM, Bangirana, P, Page, CF, Opoka, RO, Giordani, B. A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV. Neuropsychology, 2010, 24(5), 667-673.

38. Thomaidis, L, Bertou, G, Critselis, E, Spoulou, V, Kafetzis, DA, Theodoridou, M. Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study. BMC Pediatrics, 2010, 10, 99.

39. Kapetanovic, S, Leister, E, Nichols, S, Miller, T, Tassiopoulos, K, Hazra, R, Gelbard, HA, Malee, KM, Kammerer, B, Mendez, AJ, Williams, PL. Relationships between markers of vascular dysfunction and neurodevelopmental outcomes in perinatally HIV-infected youth. AIDS, 2010, 24(10), 1481-1491.

40. Dobrova-Krol, NA, van IJzendoorn, MH, Bakermans-Kranenburg, MJ, Juffer, F. Effects of perinatal HIV infection and early institutional rearing on physical and cognitive development of children in Ukraine. Child Development, 2010, 81(1), 237-251.

41. Koekkoek, S, de Sonneville, LM, Wolfs, TF, Licht, R, Geelen, SP. Neurocognitive function profile in HIV-infected school-age children. European Journal of Paediatric Neurology, 2008, 12(4), 290-297.

42. Baillieu, N, Potterton, J. The extent of delay of language, motor, and cognitive development in HIV-positive infants. Journal of Neurologic Physical Therapy, 2008, 32(3), 118-121.

43. Van Rie, A, Mupuala, A, Dow, A. Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa, Democratic Republic of the Congo. Pediatrics, 2008, 122(1), e123-e128.

44. Hazra, R, Jankelevich, S, Mackall, CL, Avila, NA, Wolters, P, Civitello, L, Christensen, B, Jacobsen, F, Steinberg, SM, Yarchoan, R. Immunologic, virologic, and neuropsychologic responses in human immunodeficiency virus-infected children receiving their first highly active antiretroviral therapy regimen. Viral Immunology, 2007, 20(1), 131-141.

45. Smith, R, Malee, K, Leighty, R, Brouwers, P, Mellins, C, Hittelman, J, Chase, C, Blasini, I. Effects of perinatal HIV infection and associated risk factors on cognitive development among young children. Pediatrics, 2006, 117(3), 851-862.

46. Nozyce, ML, Lee, SS, Wiznia, A, Nachman, S, Mofenson, LM, Smith, ME, Yogev, R, McIntosh, K, Stanley, K, Pelton, S. A behavioral and cognitive profile of clinically stable HIV-infected children. Pediatrics, 2006, 117(3), 763-770.

47. Martin, SC, Wolters, PL, Toledo-Tamula, MA, Zeichner, SL, Hazra, R, Civitello, L. Cognitive functioning in school-aged children with vertically acquired HIV infection being treated with highly active antiretroviral therapy (HAART). Developmental Neuropsychology, 2006, 30(2), 633-657.

48. Koekkoek, S, Eggermont, L, De Sonneville, L, Jupimai, T, Wicharuk, S, Apateerapong, W, Chuenyam, T, Lange, J, Wit, F, Pancharoen, C, Phanuphak, P, Ananworanich, J. Effects of highly active antiretroviral therapy (HAART) on psychomotor performance in children with HIV disease. Journal of Neurology, 2006, 253(12), 1615-1624.

49. Jeremy, RJ, Kim, S, Nozyce, M, Nachman, S, McIntosh, K, Pelton, SI, Yogev, R, Wiznia, A, Johnson, GM, Krogstad, P, Stanley, K. Neuropsychological functioning and viral load in stable antiretroviral therapy-experienced HIV-infected children. Pediatrics, 2005, 115(2), 380-387.

50. Shanbhag, MC, Rutstein, RM, Zaoutis, T, Zhao, H, Chao, D, Radcliffe, J. Neurocognitive functioning in pediatric human immunodeficiency virus infection: effects of combined therapy. Archives of Pediatrics and Adolescent Medicine, 2005, 159(7), 651-656.

51. Llorente, A, Brouwers, P, Charurat, M, Magder, L, Malee, K, Mellins, C, Ware, J, Hittleman, J, Mofenson, L, Velez-Borras, J, Adeniyi-Jones, S. Early neurodevelopmental markers predictive of mortality in infants infected with HIV-1. Developmental Medicine and Child Neurology, 2003, 45(2), 76-84.

52. Singh, KK, Barroga, CF, Hughes, MD, Chen, J, Raskino, C, McKinney, RE, Spector, SA. Genetic influence of CCR5, CCR2, and SDF1 variants on human immunodeficiency virus 1 (HIV-1)-related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. Journal of Infectious Diseases, 2003, 188(10), 1461-1472.

53. Tamula, MA, Wolters, PL, Walsek, C, Zeichner, S, Civitello, L. Cognitive decline with immunologic and virologic stability in four children with human immunodeficiency virus disease. Pediatrics, 2003, 112(3 Pt 1), 679-684.

54. Blanchette, N, Smith, ML, King, S, Fernandes-Penney, A, Read, S. Cognitive development in school-age children with vertically transmitted HIV infection. Developmental Neuropsychology, 2002, 21(3), 223-241.

55. Blanchette, N, Smith, ML, Fernandes-Penney, A, King, S, Read, S. Cognitive and motor development in children with vertically transmitted HIV infection. Brain and Cognition, 2001, 46(1-2), 50-53.

56. Baddeley, AD. Is working memory working? Quarterly Journal of Experimental Psychology, 1992, 44A, 1-31.

57. Salthouse, TA. The processing-speed theory of adult age differences in cognition. Psychological Review, 1996 103, 403-428.

58. Wood, GMO, Carvalho, MRS, Rothe-Neves, R, Haase, VG. Validação da Bateria de Avaliação da Memória de Trabalho (BAMT-UFMG). Psicologia: Reflexão e Crítica, 2001, 14(2), 325-341.

59. Couto, G. ; MENEZES, A. C. Z. ; BARRETO, Gustavo de Val ; PIRES, S. D. ; VASCONCELOS-SILVA, A. . Inteligência: perspectiva das neurociências cognitivas. Neurobiologia (Recife. Impresso), v. 74, p. 105, 2010.

# **Chapter 3** - Neuropsychological performance of young vertically infected with HIV*

Gustavo de Val Barreto[1,2,4], Virginia Nunes Viana[1,2], Jorge Andrade Pinto[3] & Vitor Geraldi Haase[1,2]

**Abstract:**

The neuropsychological impairments in vertically HIV-infected persons described in the literature as an expected event during the development and impacts on several cognitive abilities. The efforts of current studies is to identify the existence of a pattern of commitment that can guide the assessment process and intervention as well as assist in understanding the effects of the presence of HIV virus in the body over time. The objective is to describe the neuropsychological characteristics of a sample of 50 participants aged between 8 and 22 years, infected vertically divided into two groups according to the degree of the disease (HIV group and AIDS groups). It was selected a control group of 111 participants with age and education compatible with the clinical group (HIV + AIDS group). The neuropsychological assessment includes measures of intelligence, executive function, memory, motor skills and school achievement. The results show a pattern of heterogeneous commitment, being more severe in clinically most advanced group (AIDS group). Losses focus specifically on intelligence tasks, executive functions, memory and school performance. Between-subjects of clinical group (controls, HIV and AIDS) and age categories (children and adolescents) controlling for intelligence (covariate) revealed a significant effect for verbal fluency, digit span, corsi blocks and scholar skills. The results showed that individuals in the later stages of the disease (CDC class C or AIDS group) have greater impairment on neuropsychological tasks used and child group scores lower than adolescents group. The comparison of groups show that the losses obey a progressive decline as the disease progresses,

the main findings noting performance differences in the control group vs. AIDS group.

1 - Developmental Neuropsychology Laboratory, Department of Psychology, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

2 - Programa de Pos-graduacao em Neurociencias, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

3 – Departamento de Pediatria, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

3 – Centro Universitário UNA, Minas gerais, Brazil

## Introduction

The HIV virus has been increasingly common in young people around the world. In December 2014, the HIV/AIDS program of the World Health Organization estimated that there are about 36.9 (34.3 to 41.4) million people living with HIV worldwide (UNAIDS, 2015). In Brazil, there are 734.000 people living with HIV (Brasil, 2014). Vertical transmission occurs when the HIV infected mother does not make use of prophylactic measures for the prevention of HIV transmission to their child and transmission rates in Brazil are about 30% of deliveries. About 65% of vertical transmission occurs during labor and childbirth itself and the remaining 35% occur in utero (if the mother does not use ART). In addition, breastfeeding is an additional risk 7-22% transmission (Brito Sousa, Luna and Gold, 2006). With the adoption of preventive measures of child and maternal transmission, vertical transmission rates in Brazil have been reduced dramatically (about 4% of registered cases). The progression of infection in children and adolescents vertically infected follows a distinct progression than observed in infected people later. In children observe a bimodal pattern: early onset (age of onset of symptoms for about 4 months old) and late (early symptoms for about 6 years old). Rarely children vertically infected develop symptoms in adolescence.

The neuropsychological impairments in people vertically infected with HIV have been recognized since the epidemic began. Most notable has been the early manifestation of lowered of cognitive functioning due to the early central nervous system involvement, a high incidence of severe encephalopathy characterized by atrophy of the brain calcifications, spasticity and mental retardation, and the high mortality associated with the disease (Allison, Wolters & Brouwers 2009).

A significant portion of infected people experience cognitive and motor deficits, even when they use treatments aimed at controlling viral load. Literature review on the neuropsychological impairments caused by HIV show that neuropsychological impairments exist,

but the findings are heterogeneous varying according to the type of experimental design, population studied, used instruments and presence/absence of a control group for comparison of results. Several studies show no significant damage (below 2 standard deviations) associated with motor skills and other cognitive impairments (Cohen, Stege, Geursten, Scherpier, Kuijpers, Kings, Schamnd & Pajkrt, 2015; Franklin, Lim & Havens, 2007; Haase, Nicolau, Viana, Barreto & Pinto, 2014). Other studies show varying degrees of impairment to the neuropsychological functioning, more specifically losses related to memory (Keller, Venkatraman, Thomas, Deveikis, LoPresti, Hayes et al., 2004), processing speed (Haase et al., 2014), executive functions (Haase et al, 2014; Bisiacchi, Suppiej & Laverda 2000; Llorente, Brouwers, Leighty, Malee, Smith, Harris, 2012; Martin et al., 2006) and motor (Van Rie, Mupuala, Dow, 2008). Such reported neuropsychological impairments justify the importance of neuropsychological assessment specific to this population. Use only global assessment measures (like non-verbal intelligence) seem to mask the damage patterns in specific cognitive abilities.

The aim of this study is to investigate the neuropsychological characteristics of a sample of children and adolescents vertically infected, describe the pattern of observed damage and correlate the results with clinical markers of disease progression.

## Method

### Participants

There were 50 participants (with 18 in the HIV group and 32 in the AIDS group) aged between 8 and 22 years old (23 male), vertically infected, recruited from a large service care for HIV/AIDS in the city of Belo Horizonte, working in the university hospital of the Federal University of Minas Gerais. The descriptive data (mean age, standard deviation, age dispersion) are described in Table 2. A control group was recruited in the city of Belo Horizonte, comprising

111 participants (49 males). Participants in the control group were evaluated in public schools or attending in their homes according to their availability.

Participants in the clinical group (HIV + AIDS group) were invited to participate at the time attended the hospital and the assessment schedule occurred according to participant availability. Participants where evaluated in two sessions lasting about 50 minutes. All participants responded to the intelligence test and other neuropsychological measures used. A trained psychologist performed the assessment procedure. Clinical, virological and immunological data where obtained from participants in the records of the treatment center where they were invited to participate.

Exclusion criteria used was participants who have a diagnosis of peripheral neuropathy (reported by the participant or his own medical records) that may influence performance. Moreover, they are being excluded from the sample participants who submit diagnostic delay in development, mental retardation, learning disorders, physical or sensory disorders, chronic disease or movement disorders (reported by the own participant/guardian or his medical record). All of the study procedures were approved by the local ethics committee (project CAAE – 07276412.4.0000.5149)

A battery of neuropsychological tests evaluating a number of cognitive aspects, such as intelligence, executive functions, processing speed, attention, psychomotor skill and memory. In a previous study (Haase et al., 2014) using neuropsychological instruments to evaluate these functions are effective to discriminate the performance of children and adolescents vertically infected with HIV.

The three-factor model of executive functions (Fuster, 2008) inspired the selection of instruments. According to the model, cortico-subcortical circuits involving the prefrontal cortex implement the executive functions. The working memory being related to the dorsolateral prefrontal cortex, while monitoring / error detection and pulse control are related, respectively, to

the prefrontal cortex dorsomedial and ventromedial.

**Instruments**

Each participant was assessed with a comprehensive battery of neuropsychological assessment, covering this cognitive function: intelligence, executive functions, memory, motor skills and school performance (Table 1). The goal of a comprehensive assessment battery is to characterize the performance differences between different groups and identify key impairments associated with HIV.

*Raven's Progressive Matrices:* is one of the most used tools in national and international literature to assess the intelligence, especially its fluid component, wich depends minimally on formal education and socio-cultural factors. In this paper we used the two forms available for Brazil (colorfully and general scale), suitable for the investigated age group (Angelini, Alves, Custódio, Duarte & Duarte, 1999).

*School achievement test* (TDE - Stein, 1994) is the most widely used standardized test of school achievement in Brazil. The TDE comprises three subtests tapping basic educational skills: single-word reading, single-word spelling to dictation, and basic arithmetic operations. The word spelling subtest consists of 34 dictated words with increasing complexity. The arithmetic subtest is composed of three simple oral word problems that require written responses and 45 basic arithmetic calculations of increasing complexity that are presented and answered in writing. The single word reading consists of 70 single words that should be reading out loud.

*Test of attentional performance (TAP):* was developed for assessment of attention in patients with brain lesions (Zimmermann & Fimm, 1995) and aims to develop a method for evaluating the attention and its subcomponents (focused attention, divided attention and flexibility) in a simple manner and can be used in different cultures, given the nonverbal nature of the stimuli used.

Results are reported for reaction time, correct responses, errors and omissions. In this paper we used four subtests of the TAP, namely: Alert, sustained attention, go / nogo and working memory. *Alert:* The alert task aims to measure the reaction time (RT) through a visual and / or combined stimulation with auditory stimuli. *Sustained attention:* It is to focus attention on a mentally demanding activity for a period of time. In this test, a sequence of stimuli is presented on the monitor. The task is different from a working memory task for its duration (about 15 minutes) and by the need to stay focused on mental activity throughout this period. *Go-nogo:* This task consists to suppress responses in the presence of irrelevant stimuli and the response latency for the selection of the stimulus. *Working memory:* This task examines the control of the information flow and update information in working memory.

*Verbal Fluency* (VF): evaluate the controlled semantic association capacity (Moura, Simões & Pereira, 2013). The task is to generate the largest number of items belonging to a given category in a period of 60 seconds. Categories can be defined semantically or by a letter (literal fluency). The verbal fluency tasks assess the mental productivity, and the ability to regulate behavior by an arbitrary rule, monitor the mental activity avoiding repetitions and access the oral lexicon from associations restricted by rules.

*Digit span and corsi blocks:* In this digit span task is presented orally to the participant a sequence of digits that should be repeated in the same sequence (direct order); and in a second time, in reverse order (Haase et. al, 2014). The task of Corsi blocks is shown a tray 260 x 320 mm, which are set irregularly nine 40 mm x 40 blocks, numbered on the sides, so they can be identified by the evaluator and not by the participant. Sequences are presented in blocks should be repeated in the same sequence (direct order); and in a second time, in reverse order (reverse order). The procedure is similar to the repeat test of digits in the scoring criteria and suspension (Kessels, van Zandvoort, Postma, Kappelle & de Haan, 2000).

*Rey auditory verbal learning test (RAVLT):* The RAVLT assesses recent memory, learning,

interference, retention and recognition memory. The RAVLT estimates the two-tier storage capacity of 15 words each, presented in auditory modality (Malloy-Diniz, Da Cruz, Torres & Cosenza, 2000).

*Nine hole peg test (9HPT)*: The 9HPT is an assessment of manual motor skills and speed of execution of movements that require fine motor skills manual (Smith, Hong & Presson, 2000; Haase, Lima; Lacerda & Peixoto 2004; Poole, Burtner, Torres, McMullen, Markham, Marcum, Anderson & Qualls, 2005).

*Number recitation*: The articulation speed task involves two events. In the first task the numbers are recited in ascending order while the runtime is timed. In the second task the numbers are recited in descending order. Execution in descending order imposes an executive function component to task performance (Haase et. al., 2014).

**Table 1** – Summary of instruments used and cognitive functions assessed

| Cognitive domains | Tests |
|---|---|
| Intelligence | Raven Progressive Matrices |
| Executive Functions | TAP – go-nogo |
| | Verbal Fluency |
| | TAP – Sustained attention |
| | TAP – Alertness |
| | Number recitation |
| Memory | TAP – working memory |
| | Digit spam |
| | Corsi blocks |
| | Rey auditory verbal learning test |
| Motor skills | 9 hole peg test |
| School Achievement | School achievement test |

**Results**

Descriptive statistics of the participants (mean and standard deviation) are shown in table 1 according to the group (controls, HIV and AIDS). Statistical analyses was performed using version 21 of the Statistical Package for Social Sciences (SPSS). The results of participants in neuropsychological tasks were transformed into standard z scores.

Table 2 shows the characteristics of the sample studied. The intelligence results show differences into the three groups ($F=15, 70$, $p<0,001$). The *post hoc* test show that the difference are significant ($p <0,05$) for both clinical groups (HIV and AIDS).

Table 2 – Sample description

| | Variables | Controls (n=111) | HIV (n = 18) | AIDS (n = 32) |
|---|---|---|---|---|
| Age | Mean (SD) | 13,80 (3,46) | 14,56 (3,76) | 15,22 (3,17) |
| | Range | 8 – 22 | 8 - 21 | 8 – 22 |
| | Median | 14,00 | 14,00 | 15,50 |
| Sex | Male | 49 | 7 | 17 |
| | Female | 62 | 11 | 15 |
| Intelligence (Raven z score) | Mean (SD) | -0,15 (0,78) | -0,67 (0,93) | -1,01 (0,81) |
| $CD4^+$ cell count | Mean (SD) | - | 901,56 (616,11) | 672,66 (359,04) |
| $CD4^+$ % | Mean (SD) | - | 31,53 (9,24) | 27,94 (9,98) |
| Viral load | Mean (SD) | - | 9475,44 (26384,22) | 2490,81 (6845,39) |
| | Range[a] | - | 0-108207 | 0-32700 |

[a] *A viral load of zero (0) = lower than detectable.*

The sample had the following clinical characteristics at the time of data collection (between 60 days of the neuropsychological assessment). The average percentage of CD4 was 29.23% in the clinical group, the average HIV groups (32.51%) and AIDS (27.94%).

**Neuropsychological assessment**

A linear regression analysis was performed to verify the relationship between age (dependent variable) and neuropsychological variables investigated were performed. According to the results, the executive functions tasks used have a statistically significant relationship with age, indicating that some variation can be explained by the age of the participants. The phonemic verbal fluency ($F=55,13$; $p<0,001$; adjusted $R^2 = 0,252$; $\beta= 1,66$; figure 1a), semantic verbal fluency ($F = 77,28$; $p<0,001$; adjusted $R^2 = 0,327$; $\beta= 2,36$; figure 1b ), recitation of numbers - reverse - ($F = 12,71$; $p<0,001$; adjusted $R^2 = 0,074$; , $\beta= -102,89$; figure 1c), alertness ($F = 23,97$;

p<0,001; adjusted $R^2$ = 0,131; $\beta$= -11,49; ; figure 1d), sustained attention (F = 26,48; p<0,001; adjusted $R^2$ = 0,142; $\beta$= -17,711; figure 1e) and go-nogo (F = 38,25; p<0,001; adjusted $R^2$ = 0,194; $\beta$= 0,351; figure 1f). The other variables investigated are show in table 3. Due to this interaction (the effects of age on performance in the neuropsychological tasks) and to control its effect on the intra-group comparison (HIV vs. AIDS vs. controls) a division of the sample was performed in two age groups (children and adolescents) using the median age as a criterion.

Table 3 – Regressions coefficient's on neuropsychological assessment tasks

| **Test** | **F** | ***p*** | **adjusted $R^2$** | ***B*** |
|---|---|---|---|---|
| Digit spam – direct order | 20,93 | p<0,001 | 0,111 | 0,341 |
| Digit spam – reverse order | 19,95 | p<0,001 | 0,106 | 0,334 |
| Corsi blocks – direct order | 17,11 | p<0,001 | 0,091 | 0,312 |
| Corsi blocks – reverse order | 14,05 | p<0,001 | 0,075 | 0,285 |
| 9hpt – dominant hand | 14,87 | p<0,001 | 0,08 | -0,292 |
| 9hpt – nondominant hand | 8,121 | p<0,005 | 0,43 | -0,220 |
| 9hpt – both hands | 12,69 | p<0,001 | 0,068 | -0,272 |
| RAVLT – total | 13,92 | p<0,001 | 0,075 | 0,284 |
| RAVLT recognition | 16,29 | p<0,001 | 0,087 | 0,305 |
| TDE spelling | 68,19 | p<0,001 | 0,296 | 0,548 |
| TDE arithmetic | 89,37 | p<0,001 | 0,356 | 0,6 |
| TDE Reading | 20,98 | p<0,001 | 0,111 | 0,341 |

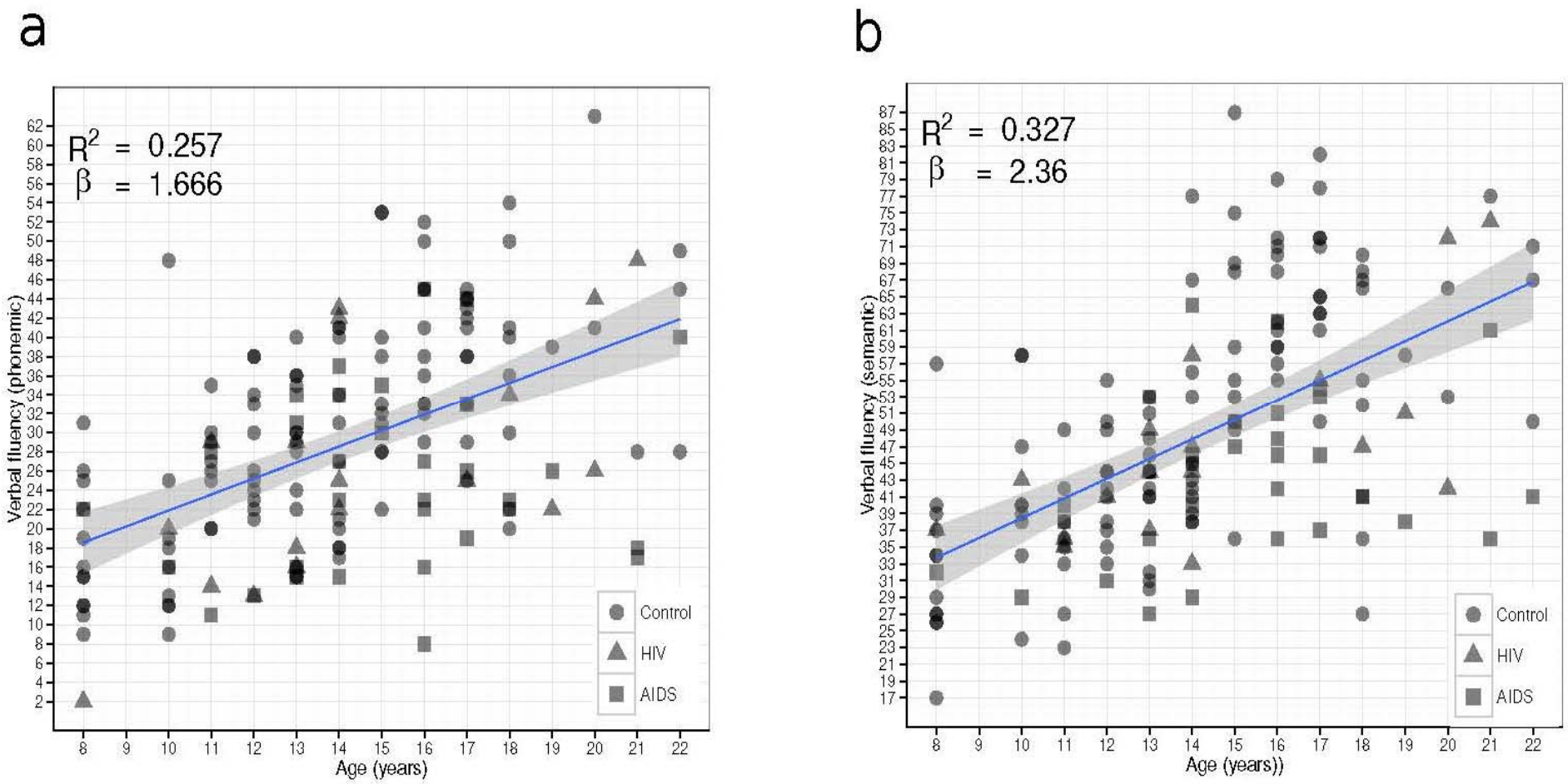



Figure 2.1 -Regression models a) phonemic verbal fluency, b ) semantic verbal fluency

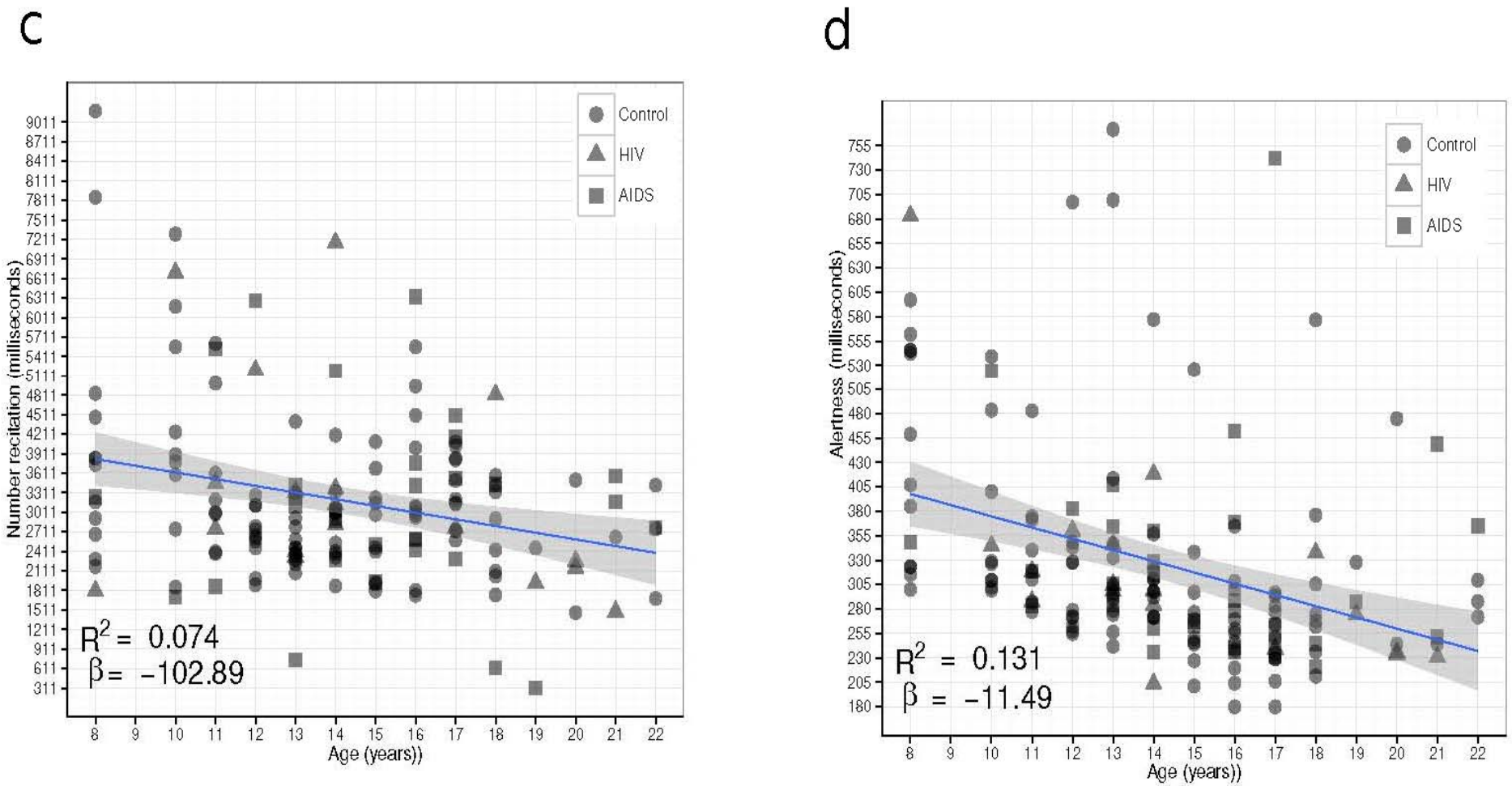



Figure 3.2 -Regression models c) recitation of numbers – reverse, d) Alertness

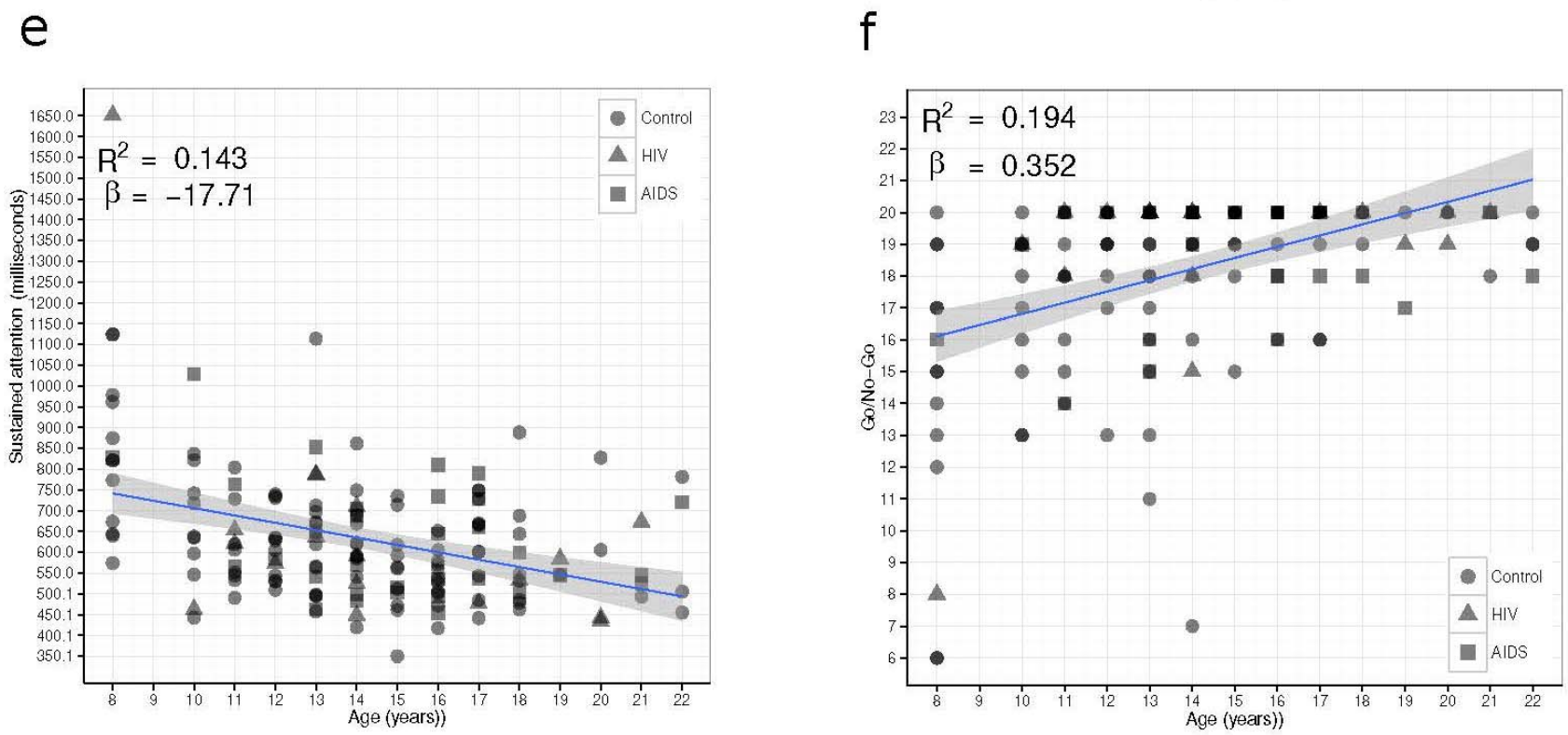



Figure 4.3 -Regression models e) sustained attention f) go-nogo.

**Analysis of covariance**

The age dispersion of the sample can lead to doubtful interpretations regarding the results, since the tasks used can be more difficult for the younger child. To control this effect, sample was divided into two groups according to the median age, constituting two age groups: children (8 to 14); adolescent (14 to 22 years). Analysis of covariance (ANCOVA) was conducted to investigate the performance between age groups (figure 2, 3 and 4) and according to the clinical stage (controls vs. HIV vs. AIDS) controlling the effect of intelligence in neuropsychological tasks (.

The results of the ANCOVA revealed a significant effect of age categories in the go/nogo, working memory, sustained attention, corsi blocks (direct order), 9hpt (dominant hand), RAVLT (total and recognition list) and TDE spelling (table 4). Also verbal fluency tasks, digit span (reverse order), TDE (arithmetic and reading) shown effects of age groups and *post hoc* comparisons between clinical groups (all $p$'s < 0,05). AIDS group consistently scores below control group and HIV group. The results in TDE's shown que the academic achievement in adolescent group is affected and that the performance of the AIDS group show worse than the other groups studied. This is an indication that the impairment of academic skills can be a cognitive *loci* compromised by the presence of the HIV.

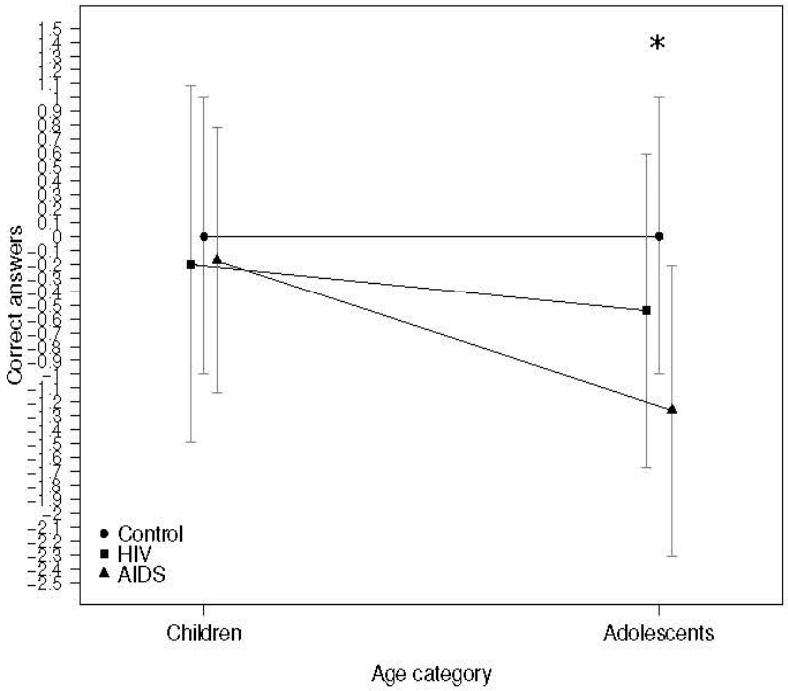
Differences in performance, even when not statistically significant, show a worse performance of the AIDS group compared to the controls and HIV group, with the exception of the results observed in the go / nogo task (figure 2c).

Table 4 – Analysis of covariance (ANCOVA) comparison between age groups and clinical groups.

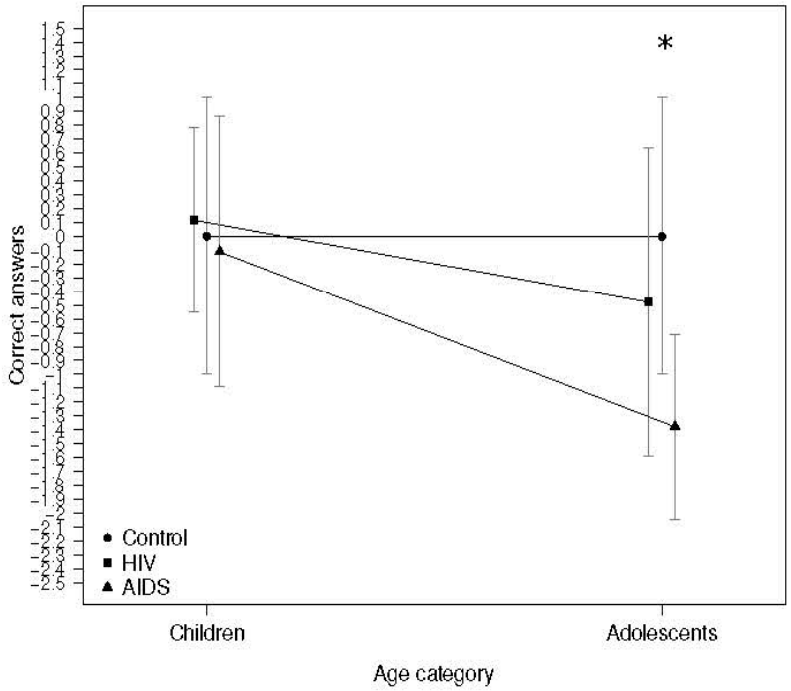
| Test | F | *P* | Post hoc |
|---|---|---|---|
| Semantic word fluency – Total correct items | 4.12 | 0.04 | a, c |
| Phonemic word fluency – Total correct items | 3.72 | 0.03 | b, c |
| Number recitation – direct order | 0.926 | 0.398 | - |
| Number recitation – reverse order | 0.082 | 0.921 | - |
| Go/Nogo | 5.50 | 0.03 | c |
| Alert | 0.190 | 0.827 | - |
| Working memory. | 14.74 | 0.001 | c |
| Sustained attentio. | 16.23 | 0.09 | c |
| digit span – direct order | 13,38 | ,000 | c |
| digit span – reverse order | 10,99 | ,000 | b, c |
| corsi blocks – direct order | 3,798 | ,012 | c |
| corsi blocks – reverse order | 3,38 | ,02 | b |
| 9hpt – dominant hand | 4,00 | ,009 | c |
| 9hpt – nondominant hand | ,853 | ,467 | - |
| 9hpt – both hands | 1,71 | ,167 | - |
| RAVLT – total | 5,21 | ,002 | c |
| RAVLT recognition | 2,81 | ,041 | c |
| TDE spelling | 10,71 | ,000 | c |
| TDE arithmetic | 35,77 | ,000 | b, c |
| TDE Reading | 4,14 | ,007 | a, c |

Legend: TDE = School achievement test, 9-HPT = Nine-hole Peg Test; a Differences between control group and HIV group; b Differences between control group and AIDS group; c Differences between child and adolescent groups.

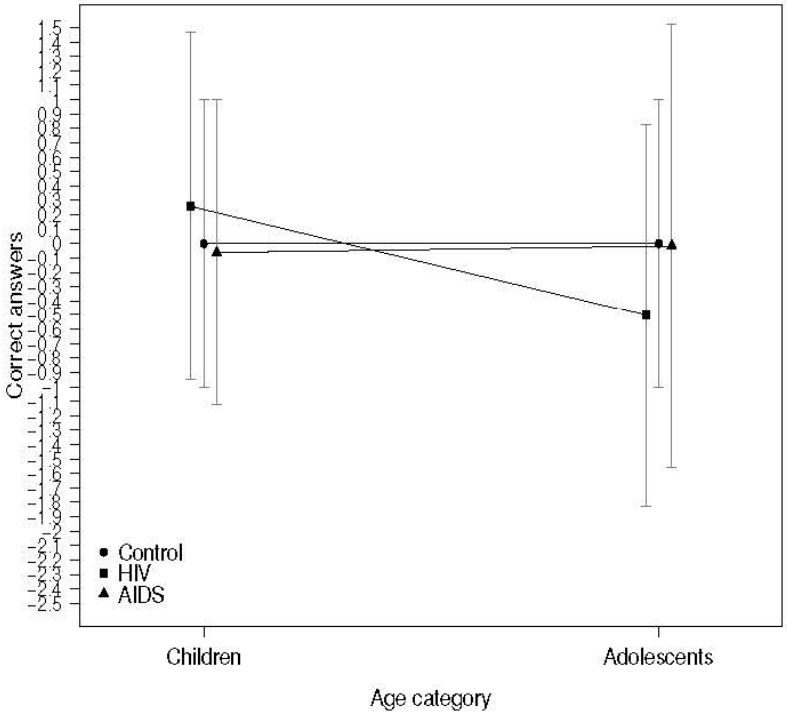
a


Correct answers
*
Control
HIV
AIDS
Children
Adolescents
Age category

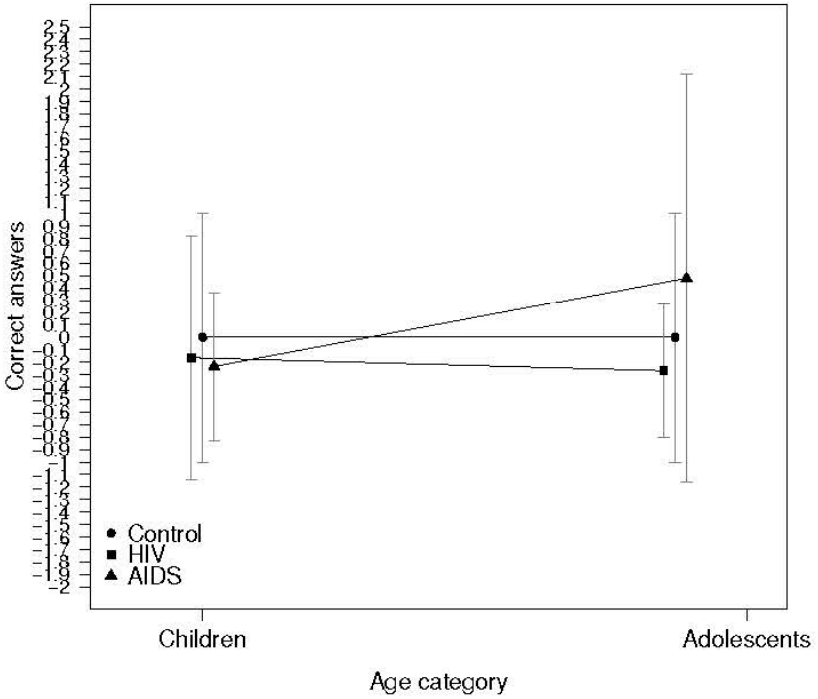
b


Correct answers
*
Control
HIV
AIDS
Children
Adolescents
Age category

c


Correct answers
Control
HIV
AIDS
Children
Adolescents
Age category

d


Correct answers
Control
HIV
AIDS
Children
Adolescents
Age category

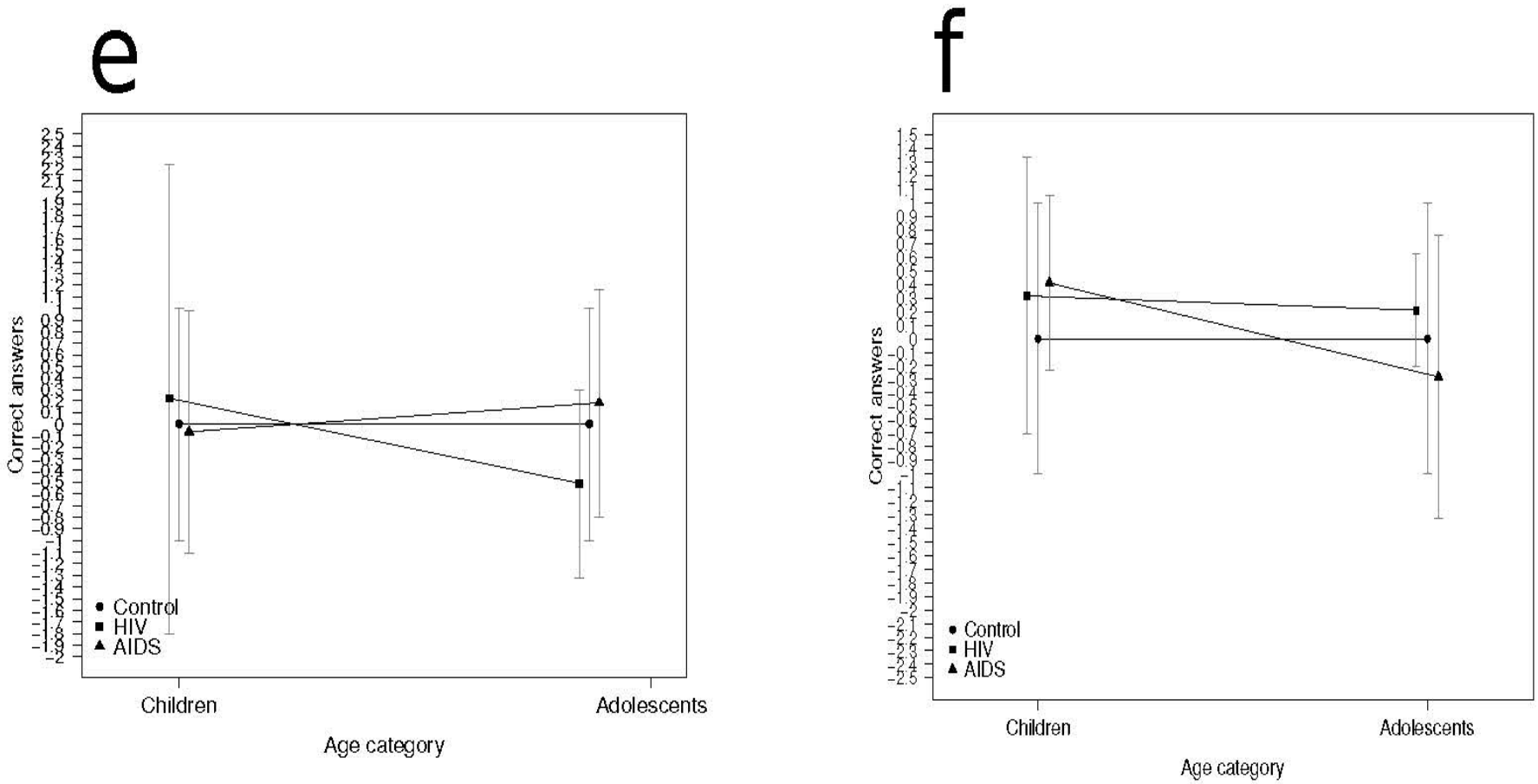
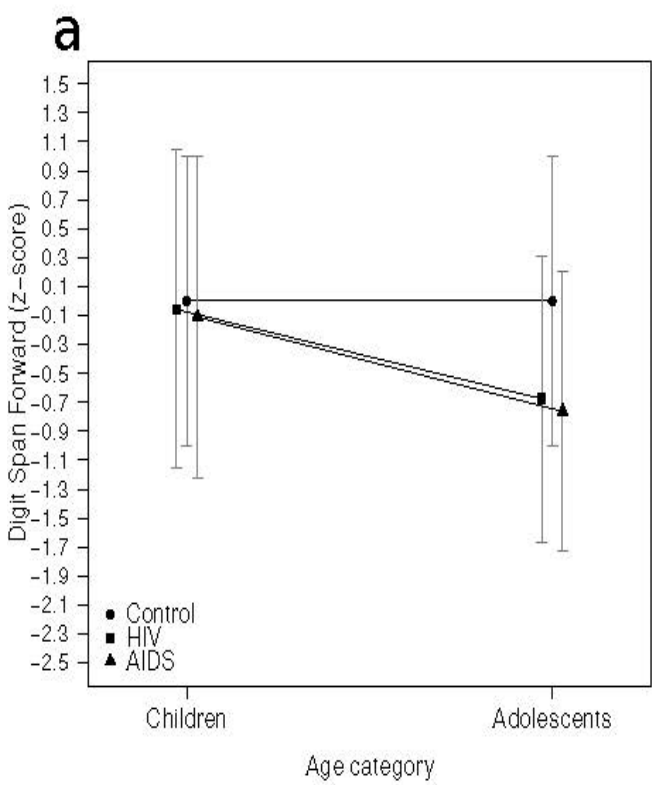
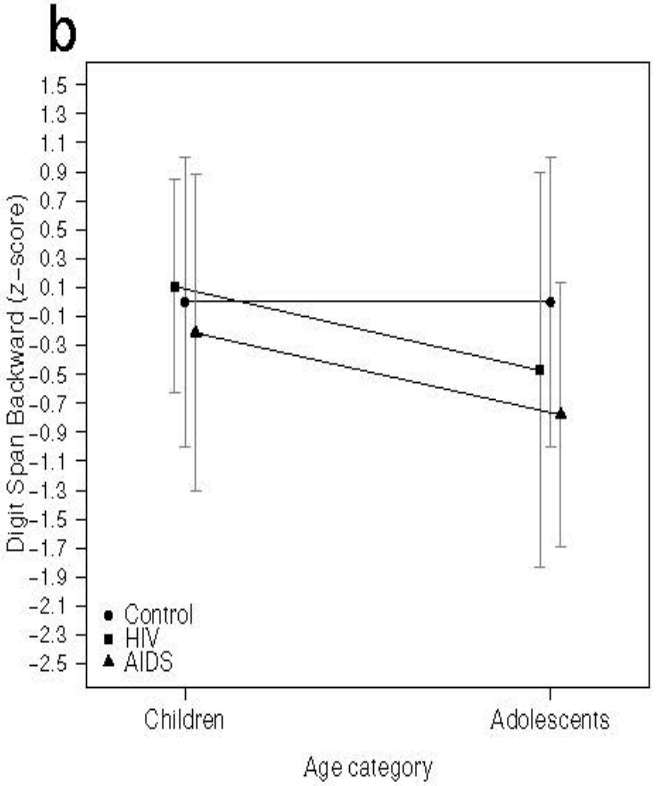



Figure 2 – Performance differences between age groups in: a) semantic word fluency task; b) phonemic word fluency task; c) go/nogo task; d) sustained attention task; e) alertness task and f) number recitation task (reverse order). * shows differences statistically significant at p<0,05


a
Digit Span Forward (z-score)
1.5
1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1
-0.3
-0.5
-0.7
-0.9
-1.1
-1.3
-1.5
-1.7
-1.9
-2.1
-2.3
-2.5
Control
HIV
AIDS
Children
Adolescents
Age category


b
Digit Span Backward (z-score)
1.5
1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1
-0.3
-0.5
-0.7
-0.9
-1.1
-1.3
-1.5
-1.7
-1.9
-2.1
-2.3
-2.5
Control
HIV
AIDS
Children
Adolescents
Age category

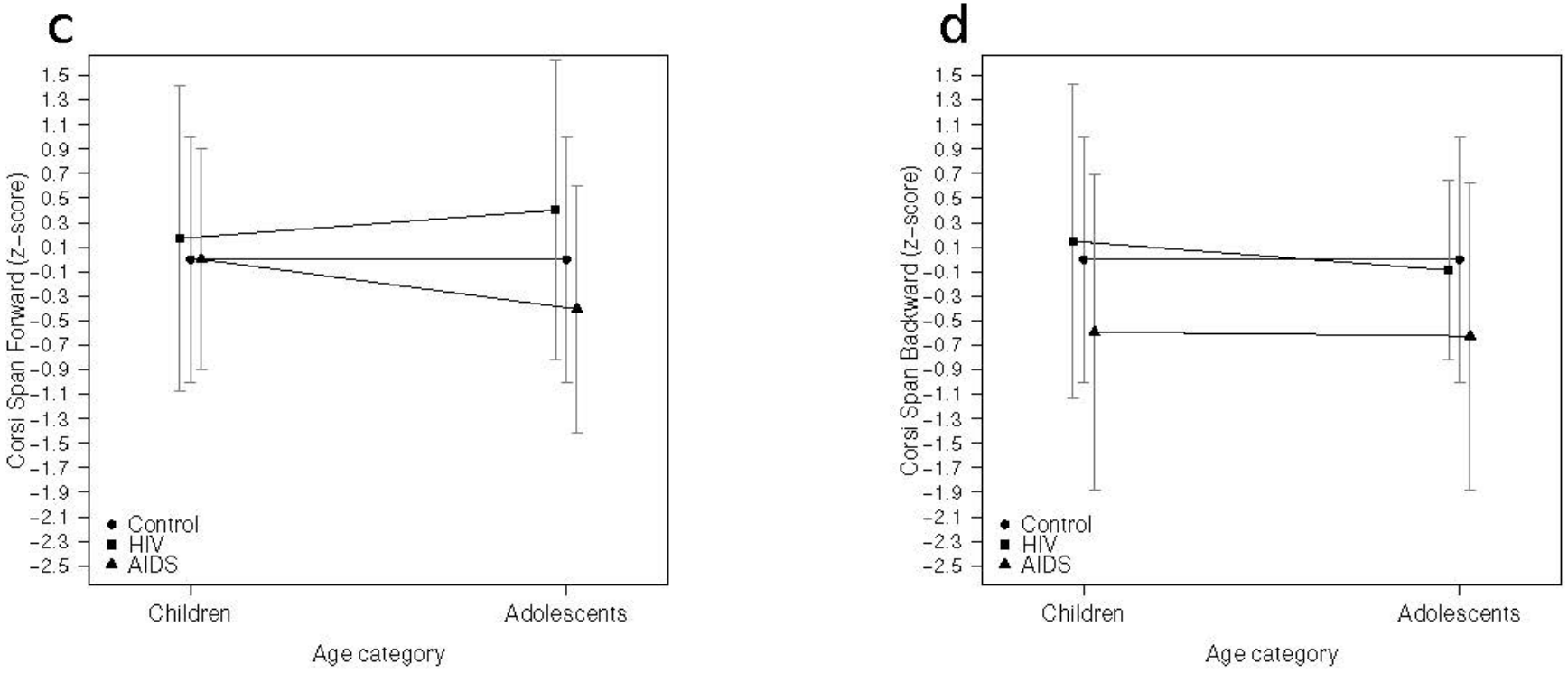



*Figure 3 - Performance differences between age groups in: a) digit span forward; b) digit span backward; c) corsi span forward; d) corsi span backward*


*Figure 4 - Performance differences between age groups in: a) TDE arithmetic; b) TDE spelling c) TDE reading.*

**Correlation analysis**

Correlation analyzes were performed between the dependent variables to determine if is associated with neuropsychological performance and clinical markers of the disease, such as CD4%, $CD4^+$ absolute and viral load.

- HIV group:

Correlation between CD4 absolute: digits direct order ($\rho$=0.552, $p<0.05$); digits indirect order ($\rho$=0.748, $p<0.001$); corsi blocks direct order ($\rho$=0.48, $p<0.05$). Cd4% was correlate with digits indirect order ($\rho$=0.539, $p<0.05$) and viral load with digits indirect order ($\rho$=-0.614, $p<0.001$)

- AIDS group:

Correlation between CD4 absolute with TDE writing ($\rho$=-0.484, $p<0.001$) and TDE reading ($\rho$=-0.447, $p<0.05$). CD % with 9hpt non dominant hand ($\rho$=0.392, $p<0.05$). Viral load had significant correlations with 9hpt non dominant hand ($\rho$=-0.422, $p<0.05$) and 9hpt both hands ($\rho$=-0.374, $p<0.05$).

**Discussion**

The aim of the study was to investigate neuropsychological characteristics of youth sample vertically HIV-infected and compares them with a demographically similar sample (control group HIV negative), and investigate whether the performance variables in neuropsychological tasks correlated with clinical measures of HIV.

There were three main findings of these results. First, is that children with HIV and AIDS perform poorly than controls in all measures used and, youth with AIDS perform poorly than youth in HIV group. The second important finding is that, apparently, there no pattern of cognitive

losses associated with immunological parameters. The third main finding is that the intelligence may be compromising over the advance of the infection and or due the decrease of other cognitive skills associated with intelligence. Such result can be attributed to the difficult of psychometrics tests of intelligence to separate the components of intelligence measures. The ART appears to reduce the size of the losses (by reducing the myelin loss associated with HIV), preventing cognitive losses, but can't improve cognitive performance (Hoare, Fouche, Phillpis, Joska, paul, Donald, Thomas and Stein, 2015).

The intellectual performance of the groups investigated, although about average, show performance differences. This demonstrates that impairment of general intelligence may be associated with the presence of the virus and its commitment pattern is subtle, evolving as the disease progresses (Haase et. al., 2014). The most obvious deficits found were in executive functions and, consequently scholar skills (like reading and mathematics). The relationship between disease progression and neuropsychological damage presents a heterogeneous pattern of impairment. Correlation results show an association between working memory and motor measures with CD4, but further data is necessary to conclude if this association is clinically significant.

The relationship of this deficit could be explained by impairment of executive function, working memory and processing speed affecting the performance in the academic skills. The impairment in arithmetic and reading skills reflects losses in related neuropsychological skills, requiring the integration skills of working memory and processing speed (Costa, Lopes-Silva, Pinheiro-Chagas, Krinzinger, Lonnemann, Willmes, Wood & Haase, 2011, Moura, Wood, Pinheiro-Chagas, Lonnemann, Krinzinger, Willmes & Haase, 2013).

The ANCOVA results show that there are performance differences that related to both age and the clinical stage of the disease. The verbal fluency tasks, as the reverser order of digit span and corsi blocks, shown to be effective in discriminating performance between age groups and

clinical groups investigated. The other variables investigated are significant performance differences between age groups but cannot find differences between clinical groups. These results may be due to the sample size of the groups.

Although there is a subtle deficit in the intelligence scores in clinical population, on average it does not exceed two standard deviations. Therefore it can not be the only cause that can explain deficit of scholastic skills and other cognitive components. The control of intelligence in the analysis of covariance also seeks to control the influence of intelligence in performance for participants, allowing infer that an brief assessment model in the neuropsychology of HIV and possessing instruments able to discriminate the cognitive performance of people with greater commitment without undergo extensive battery.

Therefore, the hypothesisis that underlying deficits, caused by the virus, such as working memory and executive functions can be responsible for the impairment of the intellectual development of children.

While few measures used to discriminate get the neuropsychological performance of the clinical sample, these results are consistent with the literature, which shows that the losses found are subtle, especially when variables related to intelligence are controlled (Haase et al, 2014; Melgarejo et al ., 2015).

**Conclusions**

The results shows that neuropsychological impairment in HIV infected population has a high frequency, including changes related executive function, working memory, attention and math/reading skills. In addition, moderate correlations between neuropsychological tasks and markers of disease progression (CD4 and viral load) found in this sample.

The population with HIV in school age are at risk for developing academic difficulties and in everyday life because of subtle deficits that manifest along the disease progression or due a secondary factors, such fatigue, frequent school absences and side effects of the medications used (Smith et al., 2004). The difficulties related executive functions, attention and memory may have indirect impact in everyday skills and bring more difficulties in the learning process.

Despite a variety of published studies emphasize the investigation of characteristics related to intelligence, the assessment of other cognitive skills, especially those related to school performance can help identify specific problems and design improvements in educational opportunities for this population specify (Smith et al., 2004).

The commitment profile found in people infected with HIV, the neuropsychological point of view, it is extremely heterogeneous. They are reported losses in executive function (Haase et al., 2014; Bisiacchi, Suppiej & Laverda 2000; Llorente, Brouwers, Leighty, Malee, Smith, Harris, 2012; Martin et al., 2006), attention (Koekkoek et al. 2008; Mellins, Brackis-Cott, Dolezal & Abrams, 2004), school performance (Smith et al., 2012; Laughton et al, 2013; (Blanchette, Smith, Fernandes-Penney & Read, 2006); Tardieu et al, 1995 Garvie et al. , 2014), memory (Keller et al., 2004; Bisiacchi et al, 2000), processing speed (Blanchette et al, 2002; Martin et al, 2006; Nachman et al, 2012; Smith et al, 2012) and low performance in intelligence tasks (Koekkoek et al, 2008; Martin et al, 2006; Nozyce, Lee, Wiznia, Nachman, Mofenson, Smith, et al., 2006; Smith et al, 2006, 2012).

The pattern of losses in the field of neuropsychology of HIV raises the question that what can be done with this population to minimize the deficits and improve quality of life without commitment of academic skills and daily activities. Such challenge is the next frontier in the field, since this established efficacy limit of ART on cognition, the attention should be concentrated in developing methods to identify and rehabilitated specific deficits in this population.

The present study has limitations that need to be considered in interpreting the results. The

sample size, the cross-sectional design, the absence of data related to treatment regimens information are limiting the generalization of the results. The small sample size of the clinical group prevents the stratification of the sample at different injury levels related to progression of the infection and its consequent neuropsychological characteristics. Future studies may emphasize that include larger samples and a longitudinal follow-up.

Another limitation consists of external variables the presence/absence of HIV infection, specifically the socio economic conditions of the brazilian reality. The differences of the population related to the type of school attended (public vs. private) may be involved in the interpretation of findings as being attributable only the presence of HIV.

The strengths of the present study deserves some qualification. The study design is a previous study improvement, with the inclusion of performance measures focused on reaction time, school performance and clinical characteristics of disease progression. The results achieved contribute to the development of a model of neuropsychological assessment that can be used in screening and identification of cognitive impairment of people served in hospitals and specialized clinics. Future studies should investigate the losses reported in the schollar skills and whether there are specific components of prejudice that enable the identification of a pattern of neuropsychological impairment and the contribution of used treatment regimens and their impact on cognitive performance.

In general, despite the losses observed in the infected group, it is necessary to recognize the effectiveness of universal access to ART program implemented in Brazil. Its effectiveness, however limited, allows young people living with HIV experience improvement of his quality of life and have more subtle impacts throughout their development.

**References**

Allison, S., Wolters, P. L. & Brouwers, P. (2009). Youth with HIV/AIDS: neurobehavioral consequences. In R. H. Paul, N. C. Sacktor, V. Valcour & K. T. Tashima, K. T. (Orgs.) *HIV and the brain. New challenges in the modern era* (pp. 187-211). New York: Humana.

Angelini, A. L., Alves, I. C. B., Custódio, E. M., Duarte, W. F., & Duarte, J. L. M. (1999). Padronização brasileira das Matrizes Progressivas Coloridas de Raven. In J. C. Raven. *Manual Matrizes Progressivas Coloridas de Raven: Escala especial*. São Paulo, SP: Centro Editor de Testes e Pesquisas em Psicologia.

Bisiacchi, P. S., Suppiej, A. & Laverda, A. (2000). Neuropsychological evalution of neurologically assymptomatic HIV-infected children. *Brain and Cognition, 43*, 49-52.

Blanchette, N., Smith, M. L., King, S., Fernandes-Penney, A. & Read, S. (2006). Cognitive development in school-age children with vertically transmitted HIV infection. *Developmental Neuropsychology, 21*, 224-241.

Brasil, Ministério da Saúde. *Boletim Epidemiológico - AIDS e DST*. Brasília: Ministério da Saúde, 2014; Ano III, n.1. [27ª a 52ª semana epidemiológica – julho a dezembro de 2013. 01ª à 26ª - semanas epidemiológicas - janeiro a junho de 2014].

Brito A.M., Sousa J.L., Luna C.F., Dourado I. Trends in maternal-infant transmission of AIDS after antiretroviral therapy in Brazil. Rev Saude Publica 2006; 40 Suppl:18-22.

Costa, A. J., Lopes-Silva, J. G., Pinheiro-Chagas, P., Krinzinger, H., Lonnemann, J., Willmes, K., Wood, G. & Haase. V. G. (2011). A hand full of numbers: a role for offloading in arithmetics learning. Frontiers in Psychology, 2, 368

Cohen S, ter Stege JA, Geurtsen GJ, Scherpbier HJ, Kuijpers TW, Reiss P, Schmand B, Pajkrt D,

(2015) Poorer Cognitive Performance in Perinatally HIV-Infected Children Versus Healthy Socioeconomically Matched Controls**.** CLIN INFECT DIS, 60 (7):1111-1119

Franklin, S., Lim, H.J., & Havens, P.L. (2007). Longitudinal behavioral and academic adjustment in children with HIV infection. *Journal of Clinical Psychology in Medical Settings, 14*, 335-343.

Fuster, J. (2008). *The prefrontal cortex* (4th. Edition). San Diego: Academic.

Garvie PA, Zeldow B, Malee K, Nichols SL, Smith RA, Wilkins ML, Williams PL. (2014). Discordance of Cognitive and Academic Achievement Outcomes in Youth With Perinatal HIV Exposure. Pediatr Infect Dis J. Sep; 33(9):e232-8.

Haase, V. G.; Nicolau, N. C.; Viana, V.N.; Barreto, G.V. & Pinto, J.A.(2014.). Executive function and processing speed in Brazilian HIV-infected children and adolescents. Dementia & Neuropsychologia, 8(1).

Haase, V. G; Lima P. E; Lacerda S. S; Peixoto L.A.M (2004). Desenvolvimento de versão Brasileira da multiplesclerosis funcional composite measure (MSFC-BCTRIMS). Arquivos de Neuropsiquiatria 62, 363-370.

Hoare, J.; Fouche, JP; Phillips, N; Joska, JA; Paul, R; Donald, KA; Thomas, KG; Stein, DJ. White mater micro-estructural changes in ART-naïve and ART-treated children and adolescents infected with HIV in South Africa. *AIDS*, *10;*29(14): 1793-801.

Keller, M.A., Venkatraman, T.N., Thomas, A., Deveikis, A., LoPresti, C., Hayes, J., et al. (2004). Altered neurometabolite development in HIV-infected children: correlation with neuropsychological tests. *Neurology*, *62*(10), 1810-1817.

Kessels, R. P., van Zandvoort, M. J., Postma, A., Kappelle, L. J., & de Haan, E. H. (2000). The Corsi Block-Tapping Task: standardization and normative data. Applied Neuropsychology, 7(4), 252-258

Koekkoek, S., de Sonneville, L. M. J., Wolfs, T. F. W., Licht, R. & Geelen, S. P. M. (2008). Neurocognitive function profile in HIV-infected school-age children. *European Journal of Pediatric Neurology*, 12, 290-297.

Laughton, B., Cornell, M., Boivin, M., & Van Rie, A. (2013). Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *Journal Of The International AIDS Society, 16*(1).

Llorente A.M., Brouwers, P., Leighty, R., Malee, K., Smith, R., Harris, L., et al. (2012). An analysis of select emerging executive skills in perinatally HIV-1-infected children. *Applied Neuropsychology: Child, 0*, 1-16.

Malloy-Diniz LF, Da Cruz MF, Torres V, Cosenza R. (2000). O Teste de Aprendizagem Auditivo-Verbal de Rey: normas para uma população brasileira. Rev Bras Neurol.; 36(3):79-83.

Martin, S. C., Wolters, P. L., Toledo-Tamula, M. A., Zeichner, S. L., Hazra, R. & Civitello, S. (2006). Cognitive functioning in school-aged children with vertically acquired HIV infection being treated with highly active antirretroviral therapy (HAART). *Developmental Neuropsychology, 30*, 633-657.

Melgarejo, M. , Pino, J. & Bassi, N. (2015). The Relationship between the Diagnosis of Human Immunodeficiency Virus (HIV) and Executive Functions in School Age Children. *Psychology, 6,* 600-605.

Mellins C.A., Brackis-Cott E., Dolezal C., & Abrams, E. (2004). The role of psychosocial and Family factors in adherence to antiretroviral treatment in HIV-infected children. *Pediatric Infectious Diseases Journal, 23*, 1035–1041.

Moura, O., Simões, M. R, & Pereira, M. (2013). Fluência verbal semântica e fonêmica em crianças: funções cognitivas e análise temporal. *Avaliação Psicológica*, *12*(2), 167-177.

Moura, R. J., Wood, G., Pinheiro-Chagas, P., Lonnemann, J., Krinzinger, H., Willmes, K. & Haase, V. G. (2013). Transcoding abilities in typical and atypical mathematics achievers: the role of working memory, procedural and lexical competencies. Journal of Experimental Child Psychology, 116, 707-727.

Nachman, S. A., Chernoff, M., Gona, P., Van Dyke, R. B., Dankner, W. M., Seage, G. R. 3rd, Oleske, J., Williams, P. L., & PACTG 219C Team (2009). Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Archives* of Pediatric and Adolescent Medicine, 163, 164-171.

Nozyce, M.L., Lee, S.S., Wiznia, A., Nachman, S., Mofenson, L.M., Smith, M.E., et al. (2006). A behavioral and cognitive profile of clinically stable HIV-infected children. *Pediatrics*, *117*, 763-770.

Poole J. L., Burtner P. A., Torres T. A., McMullen C. K., Markham A., Marcum M. L., Anderson J. B., & Qualls C. (2005). Measuring dexterity in children using the Nine-hole Peg Test. *Journal of Hand Therapy, 18*, 348-351.

Smith, R., Chernoff, M., Williams, P.L., Malee, K.M., Sirois, P.A., Kammerer, B. et al. (2012). Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *The Pediatric Infectious Disease Journal, 31*, 592–598.

Smith, R., Malee, K., Leighty, R., Brouwers, P., Mellins, C., Hittelman, J., et al. (2006). Effects of perinatal HIV infection and associated risk factors on cognitive development among Young children. *Pediatrics*, *117*, 851-862.

Smith, R.A; Matin, S.C. & Wolters, P.L. (2004). Pediatric and Adolescent HIV/AIDS. In Bronwn, Ronald T. (ed.). *Handbook of Pediatric Psychology in school Settings* (pp.195-220). New Jersey: Mahwah.

Smith, Y. A., Hong, E;, & Presson, C. (2000). Normative and validation studies of the Nine-hole Peg Test with children. *Perceptual and Motor Skils, 90*, 823-843.

Stein, L. M. (1994). *Teste de Desempenho Escolar: Manual para aplicação e interpretação*. São Paulo: Casa do Psicólogo.

Tardieu, M., Mayaux, M. J., Seibel, N., Funck-Brentano, I., Straub, E., Teglas, J. P., Blanche S. (1995). Cognitive assessment of school-age children infected with maternally transmitted human immunodeficiency virus type 1. *Journal of Pediatrics, 126*, 375-379

UNAIDS (2014). UNAIDS Report on the global AIDS epidemic. Geneva, UNAIDS, 2014.

Van Rie, A., Mupuala, A., & 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*(1), e123–e128.

Zimmermann, P., & Fimm, B. (1995). *Test for Attention Performance (TAP).* Psytest, Würselen.

**Chapter 4 -** Behavioral assessment of vertically HIV-infected Brazilian children and adolescents[†]

Gustavo de Val Barreto,[1, 2, 4] Virginia Nunes Viana,[1, 2] Jorge Andrade Pinto,[3] & Vitor Geraldi Haase[1, 2]

**Abstract**

**Objective:** Behavioral problems and psychiatric disorders are often associated with human immunodeficiency virus (HIV) infection. HIV-infected children and adolescents are at risk for developing behavioral problems, especially problems related to attention, depression, and anxiety. With the increased survival of this population, research efforts are now focusing on the long-term effects of the presence of HIV infection on both behavior and cognition. However, few studies have investigated behavioral characteristics and cognitive losses in this population. The aim of the present study was to investigate behavioral characteristics in a sample of child and adolescents vertically HIV-infected.

**Design:** cross sectional design

**Method:** This assessment design enrolled 77 children and adolescents (age range: 6-18 years) attending in a major center of treatment in the city of Belo Horizonte (Minas Gerais, Brazil) using the Child Behavior Checklist (CBCL), Raven's Progressive Matrices and investigate correlations between specific immunological and virologic indicators of HIV infection (i.e., CD4+ and viral load).

**Results:** The results revealed no significant correlations with behavioral parameters, which were within the normal range. Comparisons of subjects who were in two different stages of the

[†] The present paper was normalized according to the instructions for publication *Aids* (http://edmgr.ovid.com/aids/accounts/ifauth.htm)

evolution of infection (HIV *vs*. AIDS) indicated differences on two subscales of the CBCL (Thought Problems and Attention Problems). Significant correlations were found between the subscales of the CBCL and immunological indicators, especially viral load in AIDS group.

**Conclusion:** These results indicate the importance of using behavioral assessments to investigate specific damage that may be predictive of more serious behavioral problems throughout the development of this population and the effectiveness of AIDS program in reduce behavioral problems in this population.

**Keywords:** Children**,** Behavior, HIV, Psychological, Risk Factors

1 - Developmental Neuropsychology Laboratory, Department of Psychology, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

2 - Programa de Pos-graduacao em Neurociencias, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

3 – Departamento de Pediatria, Universidade Federal de Minas Gerais, Minas Gerais, Brazil

4 – Centro Universitário UNA, Minas Gerais, Brazil

## Introduction

In Brazil, young people with vertically acquired human immunodeficiency virus (HIV) infection have the ability to live well throughout life. The change in well-being that has occurred (i.e., with less mortality and increased survival) is attributable to the implementation of antiretroviral therapy that occurred in 1996 in Brazil [1]. Since then, the survival rate in the HIV-infected population has increased. The efficacy of antiretroviral therapy (ART) has proven extremely effective in reducing viral load and an increase in CD4+ lymphocyte count, revealing a regenerative capacity of the immune system [2].

With early diagnosis of HIV and the use of ART, the clinical course of the disease to AIDS are delayed and there has been an increase in patient survival. Research in the HIV field seeks to address the consequences of infection that develop throughout life. Such consequences include subtle cognitive deficits, specifically those that affect behavior, executive function, working memory, processing speed, and fine motor skills [2,3]. These detrimental sequelae can result in loss of the acquisition and development of academic skills. The literature reports that young people with HIV present losses in academic skills [4, 5, 6, 7, 8] compared with performance standards. Individuals with HIV infection also have a higher frequency of behavioral impairments, including anxiety and mood disorders [9, 10, 11, 12].

Neuroimaging techniques have provided ample evidence of the involvement of neurological function in the frontal cortex, basal ganglia, and their connections with other central nervous system structures. These structures have been associated with the regulation of attention, concentration, and behavior [13, 14]. However, studies of factors that are associated with developmental and behavioral problems associated with HIV infection in children are complex because of multiple influential factors, such as drug exposure during pregnancy, family conflict situations, and poverty.

The behavioral problems that are associated with infectious diseases have been of interest

in the field. The presence of an infectious disease is a risk factor for the development of behavioral disorders in children. Children with HIV often have behavioral problems, including attention-deficit/hyperactivity disorder and affective disorders. In addition to these problems that are associated with impairments in executive functions and processing speed [15, 3]. Thus, the assessment of both behavior and cognition is necessary to better understand the magnitude and extent of damage that children who live with HIV may be experiencing.

Maternal health can affect child development and behavior [16]. The prevalence of internalizing and externalizing problems in children is 16-30% in low-income families [17]. These problems can persist into adolescence and young adulthood. Internalizing problems are expressed in relation to the own subject, is characterized by symptoms of sadness, somatic complaints and fear; externalizing problems have relationship with others and presented as impulse control problems, aggression, anger and hyperactivity. Additionally, women can be dually burdened by HIV (e.g., treatment, side effects, and social effects) and anxiety and mood disorders, which are more common in females [18].

The present study investigated the occurrence of behavioral problems in children and adolescents with HIV in treatment at a major center in the city of Belo Horizonte.

## Method

### Participants

Two groups comprised the sample: (1) 25 participants with HIV infection and (2) 52 participants with acquired immunodeficiency syndrome (AIDS). The two groups were attending a major clinical treatment service in the city of Belo Horizonte (Minas Gerais, Brazil). All of the study procedures were approved by the local ethics committee (project CAAE – 07276412.4.0000.5149). The participants were assessed using the following two tasks: Raven's

Progressive Matrices [19] and the Child Behavior Checklist [20].

## Instruments

*Raven's Progressive Matrices*

General fluid intelligence was assessed using the age-appropriate version of Raven's Progressive Matrices. Two forms were validated in Brazil for different age ranges. The final scores were transformed into z-scores according to the norms listed in the manual.

*Child Behavior Checklist*

The CBCL is composed of a behavioral verification system that uses a questionnaire to assess social skills. The parents or caregivers of the participants completed the CBCL. The CBCL has a behavioral assessment scale that assesses psychopathological symptoms, with values that range from 0 to 2 (0 = absent, 1 = occurs sometimes, 2 = occurs often), noting the frequency of behaviors that occurred, on average, over the past 6 months, prior to completing the questionnaire.

Behavioral aspects were evaluated using eight syndrome scales: Anxiety/Depression, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Isolation/Depression, Rule Breaking, and Aggressive Behavior. These eight scales are grouped into three orders factors: Internalizing problems, Externalizing problems and Total Problems. The results were transformed into T scores (mean = 50, SD = 10). The standards for the instrument are multicultural and provided in the manual [20]. Clinical results are considered T scores > 70.

## Statistical analyses

All of the analyses were performed using SPSS 21 software. Demographic characteristics, HIV disease markers, and symptom frequencies were calculated for both groups. Comparisons were performed between means using *t*-tests. Correlations were evaluated between biological

markers of HIV and behavioral scores on the CBCL.

## Results

Table 1 summarizes the distribution of variables that were used in the study (i.e., demographic characteristics and z-scores on Raven's Progressive Matrices). No differences were found between groups with regard to age, sex and disease markers.

Table 1. Participant demographics, mean intelligence scores, HIV disease markers, general school achievement, and CBCL scores.

| | **HIV (*n* = 25)** | **AIDS (*n* = 52)** | ***p*** |
|---|---|---|---|
| Age (years) (mean, SD) | 12.28 (2.79) | 12.88 (3.19) | .990 |
| Age range (years) | 8-18 | 6-18 | — |
| Male | 12 | 27 | — |
| Female | 13 | 25 | — |
| **HIV disease markers** | | | |
| Cd4+ absolute (cell/$mm^3$) (mean, SD) | 867.72 (354.77) | 796.963 (398.22) | .867 |
| Cd4+ (%) (mean, SD) | 32.44 (8.54) | 29.71 (8.94) | .556 |
| Viral $load_{log}$ (mean, SD) | 7776.76 (22697.01) | 3661.73 (15605.33) | .159 |
| **Intelligence** | | | |
| Raven's Progressive Matrices (z score) (mean, SD) | -.75 (1.28) | -1.32 (1.51) | .668 |

*p* values are shown for differences between HIV and AIDS children. The data are expressed as mean and SD unless specified otherwise.

Table 2 summarizes the CBCL results. Children in the AIDS group had significantly differences on the CBCL's Thought Problems and Attention Problems scales compared with the HIV group. Overall, children in both groups had no differences. The scales that show differences between groups can be interpreted as, and behavioral variables, they are related to the fields that are related cognitive characteristics.

Table 2. CBCL T scores in HIV and AIDS groups.

| CBCL syndrome scale | Group | Mean | SD | Sig. |
|---|---|---|---|---|
| Depressive Problems | HIV | 49.60 | 12.22 | .758 |
| | AIDS | 48.67 | 12.48 | |
| Anxiety Problems | HIV | 45.91 | 11.19 | .075 |
| | AIDS | 51.22 | 12.46 | |
| Somatic Problems | HIV | 47.84 | 13.20 | .819 |
| | AIDS | 48.48 | 10.67 | |
| Social Problems | HIV | 49.47 | 9.39 | .210 |
| | AIDS | 52.37 | 9.46 | |
| Thought Problems | HIV | 47.64 | 9.76 | **.046** |
| | AIDS | 50.99 | 9.89 | |
| Attention Problems | HIV | 47.37 | 10.60 | **.038** |
| | AIDS | 52.58 | 9.88 | |
| Rule Breaking | HIV | 49.06 | 11.92 | .843 |
| | AIDS | 49.56 | 9.67 | |
| Aggressive Behavior | HIV | 53.51 | 14.82 | .534 |
| | AIDS | 51.64 | 10.89 | |
| Total Problems | HIV | 48.89 | 11.86 | .365 |
| | AIDS | 51.35 | 10.72 | |
| Internalizing | HIV | 54.40 | 12.53 | .990 |
| | AIDS | 54.36 | 12.12 | |
| Externalizing | HIV | 51.66 | 14.18 | .668 |
| | AIDS | 50.44 | 10.37 | |

*p* values are shown for differences between HIV and AIDS children. Values in bold indicate statistical significance ($p < .05$).

Significant correlations between the results of CBCL subscales and the CD4 and viral load indicators were observed. In the HIV group, the absolute CD4 count had moderate correlation with social problems subscale ($\rho$=0.535, $p<0.001$). In AIDS group the most significant correlations were observed. Moderate correlations were describe with viral load and depressive problems ($\rho$=0.397, $p<0.001$), attentional problems ($\rho$=0.42, $p<0.001$), Rule breaking ($\rho$=0.556, $p<0.001$), aggressive behavior ($\rho$=0.348, $p<0.001$), total problems ($\rho$=0.466, $p<0.001$) and externalizing problems ($\rho$=0.491, $p<0.001$). Low correlation were describe with viral load and internalizing problems ($\rho$=0.293, $p<0.05$).

**Discussion**

The present study investigated the behavioral characteristics of a sample of children and adolescents who were vertically infected with HIV. The CBCL is the most frequently used parental-report measure in clinical and research settings. Our results indicated that the children's behavior was within the normal range, with different scores on only two scales (Attention Problems and Thought Problems) between the HIV and AIDS groups. Others studies reported the emergence of behavioral problems in children with HIV [9, 11]. Recent reviews reported that children with HIV are at risk for developing behavioral and psychiatric problems [5] and maternal psychiatric symptoms could influence adherence to treatment and consequently could influence the emergence of behavioral alterations.

Significant correlations were found between CBCL and clinical markers, especially with viral load in the AIDS group. Biological markers of HIV infection are traditionally associated with subtle cognitive deficits rather than overt behavioral deficits [14]. The relationship between disease markers and behavior was investigated in the present study to evaluate the possible variance between disease progression and behavior in children. The present data show a moderate

relationship with behaviors related with depression, attentional, rule breaking and aggressive behaviors. This suggest that the increase in viral load may be related with the presence of behavioral changes, increasing the importance of adherence of ART treatments.

Cognitive impairment, although subtle, can also result in behavioral impairments [3]. In the literature, children and adolescents with HIV are considered at risk for developing psychiatric disorders. Such children have a higher incidence of mood disorders (e.g., depression), anxiety disorders, and symptoms of attention-deficit/hyperactivity disorder [9,10,11]. The presence of behavioral disorders, reported even in a small proportion in the sample, may be the initial manifestation of the observed cognitive impairments, even if the reported scores are within the normal range.

The quality of life of this population, in general, are negatively impacted by social representations associated with HIV, preconception and constant use of medications [21]. The present data may indicate that the effectiveness of the government's access to antiretroviral therapy and clinical monitoring of the infected population are reducing behavioral impairments in the HIV infected children/adolescents.

Behavioral and cognitive deficits have been observed in HIV-infected individuals since the epidemic began in the 1980s [22]. Adherence to ARTs and consequent improvements in the course of disease progression allow the observation of other changes that can occur and be ascribed to HIV infection. Cognitive impairments present a pattern of subtle impairment and can develop as clinical markers of the disease are identified, manifesting mainly in the areas of executive function, processing speed, psychomotor skills, and working memory [6, 3].

The present results indicate a relationship between behavioral impairments and biological markers of HIV infection, especially viral load in the AIDS group. The results of the behavioral assessment, on average, were within normal limits, and the group with more advanced disease (i.e., the AIDS group) had higher average scores than the group with less advanced disease

progression (i.e., the HIV group). Only two scales presented significant differences between groups (Attention Problems and Thought Problems), which is consistent with the literature [23]. Improvements in these domains in educational and clinical settings may have protective effects for this group.

Although the present findings provide insights into the behavior of children with HIV infection, some limitations of the study should be mentioned. The small sample size ($n$ = 77) makes it difficult to generalize the results. However, the present's results are comparable to other studies [9] and shows that universal access program to treat HIV/AIDS offered in Brazil has positive impacts in reducing behavioral impairments observed in this population. With the decrease of infected people and access to antiretroviral therapy behavioral problems observed at the beginning of the epidemic has diminished significantly.

In conclusion, the CBCL was useful as a multidimensional measure of behavioral problems and we suggest that it should be included in outpatient procedures in Brazil because there are no legal restrictions on its use by health professionals, and it can help identify behavioral and emotional problems in clinical settings [24]. One suggestion for future studies is to assess psychiatric symptoms and stress in parents and caregivers of children and adolescents with HIV. The presence of psychiatric disorders in parents/caregivers is a risk factor for the development of behavioral disorders in children. Mothers with indicators of depressive symptoms are more likely to have children with externalizing and internalizing problems [25] and may compromise treatment adherence [26].

**Conflicts of interest**

The authors have no conflicts of interest to declare

**References**


1. Ministério da Saúde. *Boletim Epidemiológico: AIDS e DST*. Brasília: Ministério da Saúde; 2014.
2. Smith, R A, Martin, S C, Wolters, PL. Pediatric and adolescent HIV/AIDS. In: R. T. Brown (Ed.), *Handbook of pediatric psychology in school settings*. Mahwah: Erlbaum, 2004. pp. 195-220.
3. Haase, VG, Nicolau, NC, Viana, V N, de Val Barreto, G, Pinto, JA. Executive function and processing speed in Brazilian HIV-infected children and adolescents. *Dementia and Neuropsychologia*, 2014 ***8*(1)**, 32-39.
4. Smith, R, Chernoff, M, Williams, P L, Malee, K M, Sirois, P A, Kammerer, B, Wilkins, M, Nichols, S, Mellins, C, Usitalo, A, Garvie, P, Rutstein, R. Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *Pediatric Infectious Disease Journal*, 2012; ***31***, 592-598.
5. Laughton, B, Cornell, M, Boivin, M, Van Rie, A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *Journal of the International AIDS Society,* 2013; ***16*(1)**, 18603.
6. Blanchette, N, Smith, ML, King, S, Fernandes-Penney, A, Read, S. Cognitive development in school-age children with vertically transmitted HIV infection. *Developmental Neuropsychology*, 2002; ***21***, 224-241.
7. Tardieu, M, Mayaux, MJ, Seibel, N, Funck-Brentano, I, Straub, E, Teglas, J P, Blanche S. Cognitive assessment of school-age children infected with maternally transmitted human immunodeficiency virus type 1. *Journal of Pediatrics*, 1995; ***126***, 375-379.
8. Garvie, PA, Zeldow, B, Malee, K, Nichols, SL, Smith, RA, Wilkins, ML, Williams, PL. Discordance of cognitive and academic achievement outcomes in youth with perinatal HIV exposure. *Pediatric Infectious Disease Journal*, 2014; ***33*(9)**, e232-e238.

9. Familiar, I, Ruisenor-Escudero, H, Giordani, B, Bangirana, P, Nakasujja, N, Opoka, RO, Boivin, M. Use of the Behavior Rating Inventory of Executive Function and Child Behavior Checklist in Ugandan children with HIV or a history of severe malaria. *Journal of Developmental and Behavioral Pediatrics*, 2015; ***36*****(4)**, 277-284.
10. Kerr, SJ, Puthanakit, T, Vibol, U, Aurpibul, L, Vonthanak, S, Kosalaraksa, P, Kanjanavanit, S, Hansudewechakul, R, Wongsawat, J, Luesomboon, W, Ratanadilok, K, Prasitsuebsai, W, Pruksakaew, K, van der Lugt, J, Paul, R, Ananworanich, J, Valcour, V. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. *AIDS Care*, 2014; ***26*****(11)**, 1327-1335.
11. Louthrenoo, O, Oberdoefer, P, Sirisanthana, V. Psychosocial functioning in adolescents with perinatal HIV infection receiving highly active antiretroviral therapy. *Journal of the International Association of Providers of AIDS Care,* 2014; ***13***, 178-183.
12. Nozyce, ML, Lee, SS, Wiznia, A, Nachman, S, Mofenson, LM, Smith, ME, Yogev, R, McIntosh, K, Stanley, K, Pelton, S. A behavioral and cognitive profile of clinically stable HIV-infected children. *Pediatrics*, 2006; ***117***, 763-770.
13. Aylward, EH, Henderer, JD, McArthur, JC, Brettschneider, PD, Harris, GJ, Barta, PE, Pearlson, GD. Reduced basal ganglia volume in HIV-1-associated dementia: results from quantitative neuroimaging. *Neurology*, 1993; ***43***, 2099-2104.
14. Reger, M, Welsh, R, Razan, J, Martin, DJ, Boone, KB. A meta-analysis of the neuropsychological sequel of HIV infection. *Journal of the International Neuropsychological Society*, 2002; ***8***, 410-424.
15. Wachsler-Felder, JL, Golden, CJ. Neuropsychological consequences of HIV in children: a review of current literature. *Clinical Psychology Review*, 2002; ***22*****(3)**, 443-464.
16. Carter, AS, Garrity-Rokous, FE, Chazan-Cohen, R, Little, C, & Briggs-Gowan, MJ. Maternal depression and comorbidity: predicting early parenting, attachment security, and toddler

social-emotional problems and competencies. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2001; ***40***, 18-26.

17. Qi, CH, Kaiser, AP. Behavior problems of preschool children from low-income families: review of the literature. *Topics in Early Childhood Special Education*, 2003; ***23***, 188-216.
18. Ciesla, JA, Roberts, JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *American Journal of Psychiatry*, 2001; ***158***, 725-730.
19. Angelini, AL, Alves, ICB, Custódio, EM, Duarte, WF, Duarte, JL M. Padronização brasileira das Matrizes Progressivas Coloridas de Raven. In: J. C. Raven (Ed.), *Manual Matrizes Progressivas Coloridas de Raven: escala especial*. São Paulo: Centro Editor de Testes e Pesquisas em Psicologia; 1999.
20. Achenbach, TM. *Achenbach System of Empirically Based Assessment (ASEBA): development, findings, theory, and applications*. Burlington: University of Vermont, Research Center of Children, Youth and Families; 2009.
21. Costa, TL, Oliveira, DC, Formozo, GA. Quality of life and AIDS from the perspective of persons living with HIV: a preliminary contribution by the structural approach to social representations. *Cadernos de Saúde Pública*, 2015; ***31*****(2)**, 365-376.
22. Thompson, PM, Dutton, RA, Hayashi, KM, Toga, AW, Lopez, OL, Aizenstein, HJ, Becker, JT. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. *Proceedings of the National Academy of Sciences of the United States of America*, 2005; ***102***, 15647-15652.
23. Hazra, R, Siberry, GK, Mofenson, LM. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. *Annual Review of Medicine*, 2010; ***61***, 169-185.
24. M. M. Rocha, L. A. Rescorla, D. R. Emerich, E. F. M. Silvares, J. C. Borsa, L. G. S. Araújo, M. H. S. M. Bertolla, M. S. Oliveira, N. C. S. Perez, P. M. Freitas and S. G. Assis

Behavioural/emotional problems in Brazilian children: findings fromparents' reports on the Child Behavior Checklist. *Epidemiology and Psychiatric Sciences*, 2012, pp 1-10. doi:10.1017/ S2045796012000637

25. Nöthling, J, Martin, CL, Laughton, B, Cotton, MF, Seedat, S. Maternal post-traumatic stress disorder, depression and alcohol dependence and child behaviour outcomes in mother-child dyads infected with HIV: a longitudinal study. *BMJ Open*, 2013; ***3*****(12)**, e003638.

26. Costa, LVL. *Adesão à terapia antirretroviral em crianças e adolescentes infectados verticalmente pelo HIV: Estudo prospectivo de longo prazo, coorte UFMG, 2004-2014*. Programa de Pós Graduação em Saúde da Criança e do Adolescente. Belo Horizonte: Universidade Federal de Minas Gerais; 2015.

**Chapter 5** – General discussion

Determine the degree of neuropsychological impairments in infected HIV population has been one of the recent studies goals of the virus consequences, both vertically infected populations (Haase, Nicolau, Viana, Barreto & Pinto, 2014), and adults (Geo, 2014). The main contribution of the present findings is the fact that there are losses that are attributed to the presence and progression of the clinical picture of the participants, but these losses are subtle.

The thesis aim to investigate four specific hypotheses on the impact of HIV infection:

1) there are differences in neuropsychological performance of the groups;

2) The worsening of clinical and immunological parameters of infection are associated with poorer neuropsychological performance;

3) executive functions, working memory and processing speed has a greater ability to discriminate the intra-group performance and

4) the existence of behavioral problems associated with the presence of HIV infection.

In the first study, the literature review has shown that the presence of cognitive impairment in young people with HIV is often reported in the literature. The losses involve performance decrease in intelligence tasks, executive functions, memory, attention, motor skills, visuospatial skills and language. In very young children (aged < 2 years) the use of developmental scales (that privilege the sensory motor skills) also demonstrated developmental delays in HIV infected individuals.

In study II, performance in neuropsychological tasks and school performance were evaluated. The observed results show that the losses are greater in the group with progression of infection at later stages (AIDS groups) and the group with the highest age (age > 14 years), the most prominent deficits in tasks involving executive function and school performance .

In study III the presence of behavioral changes was investigated. The presence of behavioral problems in children and adolescents with HIV, although reported in the literature, was not identified as a standard in the groups studied. On average, groups do not differ from population norms and the presence of related behavioral symptoms cannot be attributed to the presence of the HIV virus.

Together, the three studies provides some contributions to the study of neuropsychological characteristics of people infected with HIV vertically. It was reported that the loss of cognitive skills is associated with the progression of the disease and the use of ART, despite inconclusive evidence about its restorative effect of cognitive skills, by reducing the viral load decreases the size of the impact of cognitive impairments. Existing cognitive impairments have greater impact with advancing age, being observed that the performance differences are greater in the older age group. In addition, the most affected cognitive skills are general intelligence, executive function and working memory.

According to the assumptions made for the studies and the results described can be concluded that:

- Hypothesis 1: There is a difference in neuropsychological performance difference between groups (controls> HIV> AIDS);
- Hypothesis 2: The worsening of clinical and immunological parameters of infection are associated with poorer neuropsychological performance and worse performance observed in the AIDS group and moderate correlations specifically with viral load
- Hypothesis 3: The results on neuropsychological tasks of executive function, working memory and information processing speed will have greater ability to discriminate between groups. This hypothesis was partially confirmed. The working memory and processing speed tasks, more specifically computerized tasks, showed no significant

differences between groups. AIDS group observe a worse performance than other groups, but the differences are not statistically significant in all tasks. A executive function task (verbal fluency) achieved the goal of discriminating performance between clinical groups and age groups.

- Hypothesis 4: There is lower performance assessment in children and adolescents with HIV. This hypothesis was not confirmed. We have not found evidence of behavioral changes in the sample.

The AIDS pediatric commitment profile suggests that the losses begin in motor skills (Le Doaré, Bland & Newell, 2012; Pearson McGarth, Nozyce, Nichols, Raskin, Browers, Lifschitz, Baker and Englund, 2000), progressing to loss of processing speed and executive functions (Haase, Nicolau, Viana, Barreto & Pinto, 2014 ), memory and school performance (Koekkoek, Sonneville, Wolfs, Licht & Geelen, 2008). Such losses, although subtle, bring losses in the academic and social life of those infected.

Uma das preocupaçoes atuais no context nacional e o aumento de adolescents infectados atraves de via sexual, em especial as mulheres, sendo consideradas um grupo de risco nessa faixa etária e que aumenta a possibilidade do numero de adultos infectados e consequentemente o numero de indivíduos contaminados verticalmente.

Academic performance is a standard by which the success of the individual is assessed. They are expected of young people with HIV that they meet the established academic standards, regardless of variables related to disease that may interfere with their performance. Thus, it is essential to understand how academic performance relates to their overall cognitive development considering the deficit factors that may mediate and help in understanding how to better prepare and help young people with HIV to be able to develop their overall academic potential.

The development of longitudinal studies, involving clinical, immunological and

neuropsychological parameters may contribute to understanding the mechanisms of interaction between cognitive development, presence of HIV and the impact of ART on prevention and maintenance of the cognitive status of people.

**References**

Geo, L. A. (2014). Frequencia, correlatos e perfil neuropsicológico do transtorno da cognição associado com a infecção pelo HIV. Dissertação de mestrado apresentado no programa de pos graduação em Neurociências da Universidade Federal de Minas Gerais.

Haase, V. G.; Nicolau, N. C.; Viana, V.N.; Barreto, G.V. & Pinto, J.A. (2014.). Executive function and processing speed in Brazilian HIV-infected children and adolescents. *Dementia & Neuropsychologia, 8*(1).

Koekkoek, S., de Sonneville, L. M. J., Wolfs, T. F. W., Licht, R. & Geelen, S. P. M. (2008). Neurocognitive function profile in HIV-infected school-age children. *European Journal of Pediatric Neurology*, 12, 290-297.

Le Doaré, K., Bland, R & Newell, L. (2012). Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. *Pediatrics, 130* (5), e1326-44.

Pearson, D. A., McGrath, N. M., Nozyce, M., Nichols, S. L., Raskino, C., Brouwers, P., Lifschitz, M. C., Baker, C. J. and Englund, J. A. (2000). Predicting HIV disease progression in children using measures of neuropsychological and neurological functioning. Pediatric AIDS clinical trials 152 study team. *Pediatrics; 106* (6).

Apendix – **Termo de aprovação do comitê de ética em pesquisa (COEP-UFMG)**

UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP

**Projeto: CAAE – 07276412.4.0000.5149**

**Interessado(a): Prof. Vitor Geraldi Haase**
**Departamento de Psicologia**
**FAFICH- UFMG**

**DECISÃO**

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 05 de setembro de 2012, o projeto de pesquisa intitulado **"Funções executivas e velocidade de processamento em crianças e adolescentes HIV infectadas"** bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

**Profa. Maria Teresa Marques Amaral**
**Coordenadora do COEP-UFMG**

*Av. Pres. Antonio Carlos, 6627 – Unidade Administrativa II - 2° andar – Sala 2005 – Cep:31270-901 – BH-MG*
Telefax: (031) 3409-4592 - e-mail: coep@prpq.ufmg.br