Testing Techniques in the Evaluation of Severity of HIV-Associated Neuro-Cognitive Disorder in Children

Saida N. Saidkhodjaeva[1], Yokutkhon N. Majidova[2], Asal N. Abduvakhitova[3], Umida U. Abdullaeva[4]

[1]PhD, Associate Professor, Department of Neurology, Pediatric Neurology and Medical Genetics, Tashkent Pediatric Medical Institute, 223 Bogishamol Street, Tashkent, Uzbekistan, [2]PhD, DcS, Professor, Head of the Department of Neurology, Pediatric Neurology and Medical Genetics, Tashkent Pediatric Medical Institute, 223 Bogishamol Street, Tashkent, Uzbekistan, [3]Assistant of the Department of Faculty Internal Medicine, Professional Pathology, Hospital of Internal Diseases and Propaedeutic of Internal Diseases, Tashkent Pediatric Medical Institute, 223 Bogishamol Street, Tashkent, Uzbekistan, [4]PhD student of the Department of Epidemiology, Infectious Diseases, Tashkent Pediatric Medical Institute, 223 Bogishamol Street, Tashkent, Uzbekistan

Abstract

Introduction: The number of HIV infected children exceeds 3 million worldwide. The most severe clinical manifestations and complications of the disease are HIV-associated neurocognitive disorder and HIV encephalopathy. These factors make the scientists search for method of optimizationin the diagnosis of neuro-HIV and identifying various pathological processes that determine the clinical course.

Materials and Method: 154 children were tested with HIV diagnosis. All patients were examined for neurological, psychological and cognitive disorders. Quality of life of sick children were examined by the questionnaire of PedsQL. In order to compare the results, study included 20 healthy adolescents (control group - CG), who also tested using the above method. Using the MS Excel software average values summarized and their standard deviations were calculated.

Results: All patients were diagnosed with 3rd and 4th stages of HIV. HIV-associated neurocognitive disorder: grade 2 in 100 patients – 64.94% and grade 3 - in 54 patients - 35.06%. Epilepsy was diagnosed in 31 patients, peripheral polyneuropathy in 7, vacuolar myelopathy in 8, and consequences of acute cerebrovascular accident in 9 with focal neurological deficit in 2. The Raven test: average test result was 18.68±4.51%. Aggressive behavior: negativism prevailed in 74 patients, and in 11 cases (7.14%) it was combined with physical aggression, and in 12 cases (7.79%) - with resentment. In addition, indirect aggression was detected in 18 patients (11.69%), resentment in 41 patients (26.62%), suspiciousness in 10 patients (6.49%), and 19 patients (12.34%) - irritation. Quality of life questionnaire revealed difficulties associated with physical activity (18.30±4.51 with maximum score of 32 points), with emotional states (15.50±2.23 with maximum of 20), social activity (14.10±2.93 with maximum of 20) and life in school (19.29±1.23 with maximum of 20).

Conclusion: HIV-associated neurocognitive disorder is manifested by a deterioration in intelligence, various forms of aggressive behavior and is associated with a decrease in the quality of life in terms of physical, emotional, social activity and learning at school.

Keywords: *HIV infection, HIV-associated neuro-cognitive impairment, children, quality of life.*

Introduction

About 3.4 million children worldwide are infected with the human immunodeficiency virus (HIV)/ AIDS. A significant part of them who have indications for antiretroviral therapy does not receive it today (UNAIDS, 2012)[1]. Neurological manifestations of HIV infection are common in both children and adults. A wide range of neurological conditions can be caused by the HIV, however, damage of the central nervous system

due to this virus, which affects the development of the brain in the embryo and baby, leads to the most severe complication of damage to the nervous system - HIV encephalopathy. In children not receiving treatment, the prevalence of the disease varies from 20% to 60% (Donaldet al, 2015; Foster et al, 2006 and Van Rie et al, 2007)[2]. The range of neurological complications that occur in children infected with HIV is quite wide and complex. One of the most common manifestations is HIV-associated neurocognitive disorder. In 18% of patients infected with HIV, it is the first clinical manifestation of AIDS (Saidkhodjaeva et al, 2019)[3];in 12 – 23 percent of them develop severe encephalopathy, usually during the first year of their life (Van Rieet al, 2008; Chiribogaet al, 2005; and Tardieu et al, 2000)[4]; in 35-50 percent of those children will develop encephalopathy in the future (Van Rie et al, 2007)[5]; in 50–90 percent of all HIV-infected infants and children develop anti-retroviral therapy deficiency (Kovacs, 2009).[6] Behavioral disorders are observed in 35 percent of all HIV-infected patients (Govenderet al, 2011), psychiatric manifestations - in 48-61 percent (Mellinset al, 2006; Wood et al, 2012; and Musisi et al, 2009).[7]

HIV affects the central nervous system shortly after the onset of systemic infection. Penetration into the central nervous system is largely mediated by infected macrophages-monocytes or $CD4^+$-T-lymphocytes (the effect of a Trojan horse), or both. Viral replicas isolated in the brain are predominantly CCR5-trophic, suggesting that virus invasion is driven by monocytes (Kramer-Hämmerleet al, 2005 and Banks et al, 2006). Once it penetrates the central nervous system, HIV basically infects perivascular macrophages and microglia, and blocks the proliferation of nerve progenitor cells. The expression of inflammatory neurotoxic neurotransmitters occurs in various types of CNS cells. Pathological changes include the formation of microglial nodules and large multinucleated cells, reactive astrogliosis, and the loss of a specific subpopulation of neurons. Damage and death of neurons are caused by several direct and indirect pathogenetic mechanisms. The consequences are the development of neurological and neurocognitive disorders.

These factors make us look for approaches to optimizing the diagnosis of neuro-HIV and identifying various pathological processes that determine the clinical picture (Mellinset al, 2006)[8]. Children with particularly weak cognitive and psychomotor functioning were most at risk of developing the disease. Prospective observational studies have found that significant neurocognitive impairment leads to a worse outcome of the disease and an increased risk of death, even against the background of combined etiological and pathogenetic treatment (Pearson et al, 2000).[9] Compared to healthy children, HIV-infected children have a much weaker development of early motor and cognitive skills. Although no clinical or clinical prognostic prediction scheme has yet been proposed, risk factors associated with HIV encephalopathy include maternal and child immune status, high plasma viral load, high levels of circulating monocytes, infection time, transmission route, and treatment options at an early stage (Le Doaréet al, 2012 and Abubakar et al, 2008).[10]

A study in the Democratic Republic of Congo examining the effect of HIV on the development of the nervous system in preschoolers found that HIV-infected children had a severe delay in cognitive function, motor skills, speech, and understanding[11]. Illustrating the complexity of the etiology of HIV-related cognitive and behavioral problems, the study also found that AIDS-infected orphans and HIV-negative children whose mothers had AIDS show a strong delay in their neurocognitive development, albeit to a lesser extent, in the area of development. than HIV-infected children (Van Rie et al, 2008)[12]. A review article of all studies in South Africa, evaluating the development, knowledge and behavior of HIV-infected children as their primary outcome, found evidence of a delay in cognitive function, speech and motor skills in children suffering from HIV[13]. However, this article also emphasizes the lack of information in this area, as well as the fact that almost all studies focus on a group of preschool children[14]. Also, according to the results of the study, it was shown that HIV affects all areas of the child's functioning, motor development is most obvious in terms of severity, early onset and resistance in all age groups. However, the development of motor skills was the most widely evaluated area, while the development of the language was less vigorously evaluated, therefore an accurate quantitative assessment of the effect cannot yet be made. (Abubakar et al, 2008).[15]

Purpose of the study is to evaluate the diagnostic significance of various testing method in assessing the severity of HIV-associated neuro-cognitive impairment in adolescent patients.[16]

Materials and Method

Study Population: The study included 154 children (92 boys - 59.74% and 62 girls - 40.6%) who are registered with HIV infection and are hospitalized in a Specialized Clinic of Infectious Diseases of the Republican AIDS Center (Tashkent, Uzbekistan) and receiving antiretroviral therapy (HAART). The mean age of the patients was 14.53±1.58 years (12-18 years), the duration of HIV diagnosis was 7.05±3.36 years (1-13 years), the duration of antiviral therapy was 6.41±3, 47 years old (1-13 years old). In 23 patients (14.94%), the vertical route of infection was diagnosed, and non the mother took HAART during pregnancy. In other children, the infection pathway is identified as parenteral. The average virus concentration was 345.85±181.45 copies/ml, while in 23 patients (14.94%) HIV RNA in the blood was not determined. The average number of $CD4^+$ cells was 461.91±230.32 in 1 mm^3 of blood.

Neurological Examination: A neurological study included a standard neurological examination, including an assessment of consciousness and some mental functions (speech, praxis, gnosis), functions of the cranial nerves, the state of the motor and sensory spheres, the autonomic nervous system, as well as neurophysiological and neuroimaging method of research (electroencephalography and magnetic resonance imaging).

Psychological and cognitive examination: All patients included in the study underwent the test aimed for studying the psychological and cognitive status, including test method: "The Raven progressive matrix scale" (state of intelligence), the Bass and Darki test modified by G.V. Rezapkina (diagnosis of various forms of aggressive behavior), and a pediatric quality of life questionnaire (PedsQL) for adolescents 13-18 years old.[17]

Intelligence Test: The Raven test, proposed for assessing the level of intelligence, is based on the use of the ability to learn based on the generalization of one's own experience and the creation of schemes to handle complex events, logical thinking. This test, convenient in application and simplicity in interpretation, repeatedly confirmed high indicators of validity and reliability.[18] The test allows it is not associated with linguistic abilities and skills and does not depend on the level of education. The Raven matrix consists of 60 images combined into 5 matrices, in each of which it is necessary to select the missing fragment, using the identified patterns.[19] In each matrix, tasks are progressively complicated. test tasks are performed without time limit, but it is noted how many tasks are completed correctly in the first 20 minutes. Thus, the Standard Progressive Raven Matrices test can be used both as a speed test (with time constraints on task execution) and a performance test (without time constraints).[20] The choice of the test application regimen should be made depending on the purpose and diagnostic conditions (first of all, the possibility of ensuring long-term continuous work of the test subject). The assessment is the percentage of correct answers, expressed as a percentage. Interpretation of the test allows us to distinguish 5 degrees of intellectual development: 1st degree - more than 95% - high intelligence; 2nd degree - 75-94% - intelligence is above average; 3rd degree - 25-74% - average intelligence; 4th degree - 5-24% - intelligence is below average; 5th degree is a defect.[21]

Test for behavior: Bass-Darki test, modified by G.V. Rezapkina, proposed in 2006, allows you to diagnose various types of aggressive behavior. The test includes 35 statement questions. The test subject is invited to apply the statement to patients.[22] If he reacts in a similar way, the answer is assigned 1 point. During the interpretation, all issues are divided into 7 forms of aggression. The form that received more than 3 points is recognized as dominant in the subject. According to the test results, the following forms of aggressive behavior are distinguished: physical aggression (statements 1,8,15,22,29), indirect aggression (2,9,16,23,30), irritation (3,10,17,24,31), negativism (4,11,18,25,32), resentment (5,12,19,26,33), suspiciousness (6,13,20,27,34), verbal aggression (7,14,21,28, 35).[23] The test is based on self-esteem. Its accuracy depends on the frankness of the subject. According to the results of the testing (increased level of aggression, inability to control emotions, etc.), it is not recommended to choose professions related to communication, maintenance, education, training - that is, all professions related to people. Low values for this test testify to your delicacy, pliability and non-conflict. However, these indicators may indicate a lack of perseverance in achieving their goals and defending their position.[24]

Quality of life Examination: The study of the quality of life of children is a new topical area of interdisciplinary research in domestic health care. The development of a methodology for studying the quality of life in pediatrics opens up the possibility of a comprehensive analysis of the physical, psychological

and social functioning of children. For this, our study used the pediatric quality of life questionnaire PedsQL, version 4 (for children aged 13-18), published in 1998 and translated into Russian, includes 23 situations that describe physical, emotional, social activity and school life. The questionnaire is recommended for studying the quality of life of healthy and sick children; using these tools, normative indicators of quality of life for the child population can be obtained. The use of the created tools in children with various diseases allows to expand knowledge about the attitude of children of a given age to their own health problems, treatment, degree of satisfaction with treatment; opens up new possibilities for assessing the impact of various diseases on the physical, psychological and social functioning of sick children. The test subject is asked to rate how each of these situations created difficulties in the past month. At the same time, 0 points are assigned to a situation that has never created difficulties, 5 points - in the case of constant difficulties with the described action. Thus, the maximum score for each situation is 5 points (almost impossible activity), the minimum score is 0 (no difficulty). The maximum score in terms of physical activity is 32 points, emotional social and complex activity is 20 points, the total maximum score is 92 point.

For comparison, the study included a group of 20 healthy adolescents of comparable age (control group - CG), who also tested using the above method.

Statistical Analysis: All data was entered into the software of MS Excel tables to calculate average values and their standard deviations. Intergroup difference was evaluated using Student's t-test for 2 comparisons. Frequency comparison was carried out using the chi-square table criterion.

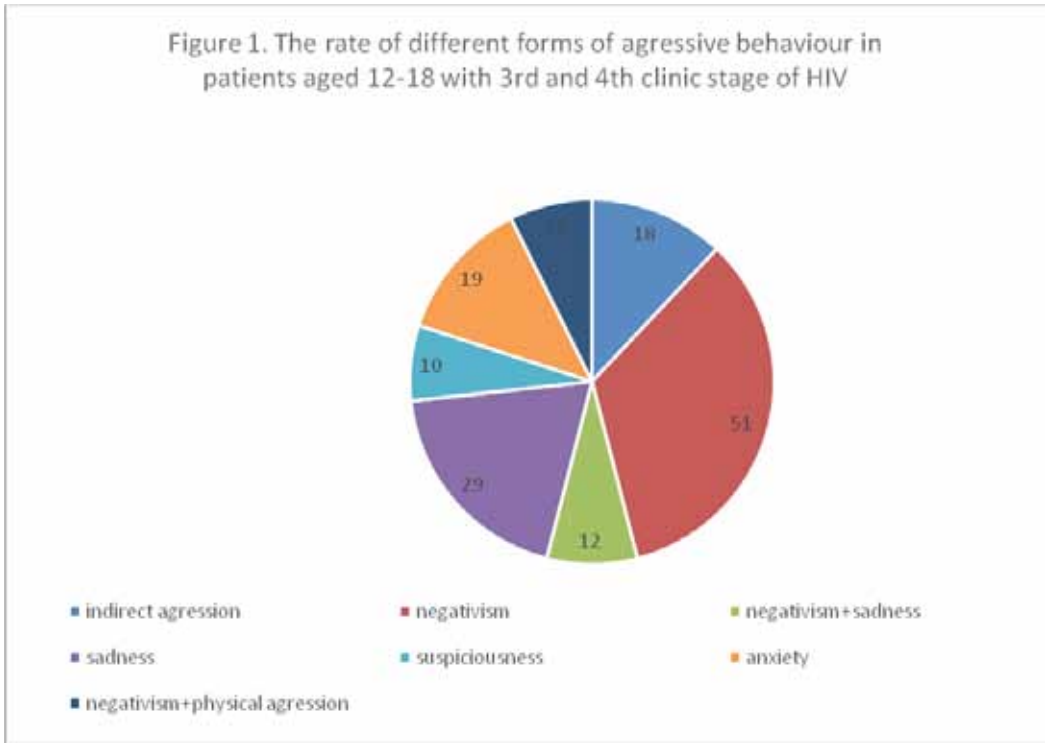
Results

During the study, all patients were diagnosed with 3rd and 4th (77 patients each — 50%) clinical stages of HIV infection involving the nervous system disorders in the form of an HIV-associated neurocognitive disorder (grade 2 in 100 patients — 64.94% and grade 3 - in 54 patients - 35.06%). In addition, epilepsy (20.13%) was diagnosed in 31 patients, peripheral polyneuropathy (4.55%) in 7 patients, vacuolar myelopathy (5.19%) in 8 patients, and consequences of acute cerebrovascular accident in 9 patients with focal neurological deficit (5.84%), in 2 patients - the consequences of herpetic meningoencephalitis (1.30%).

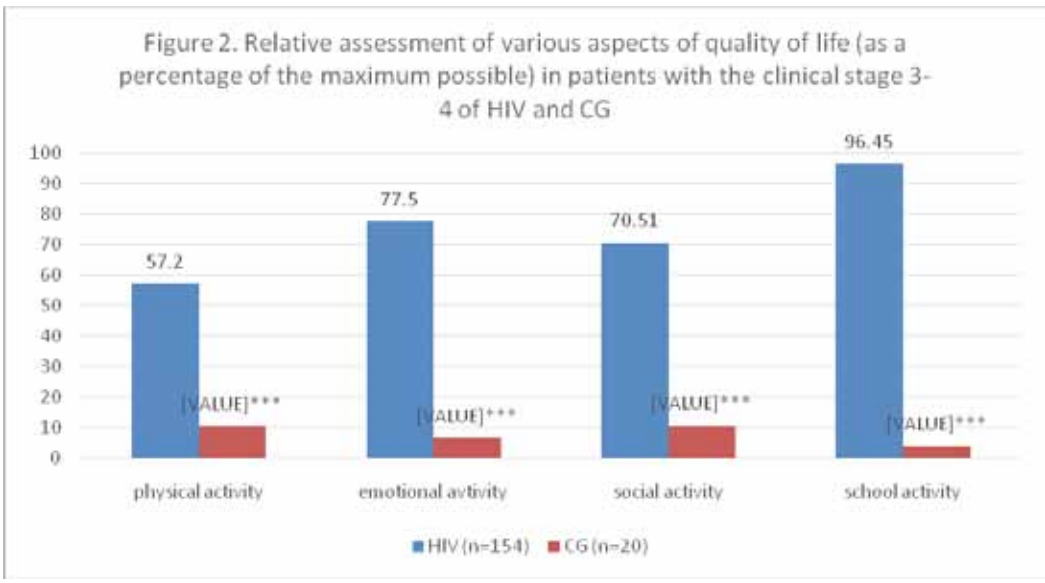
A neurological examination revealed a syndrome of autonomic dysfunction with impaired skin innervation and functional disorders of the gastrointestinal tractin 142 patients (92.21%), coordinating disordersin 96 patients (62.34%), in 52 patients (33.77%) focal motor disorders, including hemiparesis, in 22 patients (14.29%), in 48 patients (31.17%) speech disorders and elements of apraxia were noted, in 32 patients (20.78%) - insomnia and parasomnia syndromes. At the time of the examination, all patients were diagnosed with a lag in psycho-motor development, although in the period of 1-3 years these disorders were detected only in 26 patients (16.88%). Convulsive syndrome was diagnosed and confirmed by electroencephalography in 11 patients (7.14%).

The test using the Raven progressive matrix scale revealed a significant decrease in the intellectual level in the patients included in the study: the average test result was 18.68±4.51%, with a spread from 6 to 26%. At the same time, in 8 patients (5.19%) the indicator was within the boundaries of average intelligence (25-74%), in the remaining patients (146 patients - 94.81%) - below the average (5-24%). In the CG, the average score obtained in the Raven test was 52.31±4.38% ($p<0.001$, the significance of the difference with the index of the main group).

Some forms of aggressive behavior were observed in all patients included in the study (Fig. 1), while, according to the Bass and Darka test in the modification of Rezapkina, negativism prevailed (74 patients - 48.05%), and in 11 cases (7.14%) it was combined with physical aggression, and in 12 cases (7.79%) - with resentment. In addition, indirect aggression was detected in 18 patients (11.69%), resentment in 41 patients (26.62%), suspiciousness in 10 patients (6.49%), and 19 patients (12.34%) - irritation. Indirect aggression (5%) was found in CG in 1 teenager, negativism in 3 (15%) and resentment in 2 (10%) ($p <0.001$ significance of the frequency of aggressive behavior between the main and CG according to the tabular chi-square criterion).



The quality of life questionnaire, adapted for adolescents 13-18 years old, revealed difficulties associated with physical activity (18.30±4.51 points with a maximum score of 32 points, Fig. 2), with emotional states (15.50±2.23 points with a maximum of 20 points), social activity (14.10±2.93 points with a maximum of 20 points) and life in school (19.29±1.23 points with a maximum of 20 points). For an objective assessment of the quality of life in patients with HIV infection, CG was included in the study, in which the average quality of life scores were 3.27±0.26 (difficulties associated with physical activity), 1.28±0.07 points (difficulties associated with emotional state), 2.11±0.03 points (difficulties associated with social activities) and 0.74±0.02 points (difficulties associated with school activities, p <0.001, significance of differences with the average value in the main group for all four parameters).



Note: *** - significance of differences between HIV and CG groups p <0.001.

Discussion

There are several neuropsychological and neuroimaging studies of HIV-positive children with a safe CD4 count (more than 25%). A neuro-visual study found that such children showed far worse results than an HIV-negative control group using the Wechsles Abberviated Scales of Intelligence Verbal and Preformance IQ test and standardized testing of visual-spatial processing of information, visual memory, and executive functions [21], which found in this study in adolescents with 3-4 stages of HIV infection. Significant motor and cognitive impairments were also found in HIV-infected children[22]. HIV in older children is currently associated with more narrow and specific cognitive impairments, including difficulties in visual-spatial and motor integration, memory lapses, impaired attention, speech and socio-emotional deficit [23]. These features (in particular, violations of the executive function) can lead to profound functional impairment in the classroom.

Adult literature on HIV-related CNS damage supports a range of HIV-related neurocognitive disorders, including HIV-related dementia, mild neurocognitive disorder, and asymptomatic neurocognitive impairment [24]. The criterion is clinically useful, since it takes into account the conceptualization of a number of functional disorders and helps to formulate an individual treatment plan for adult patients with HIV-related problems. Similar spectrum criteria are needed in the case of HIV in children in order to better understand the effect and the social and educational management needed to support children infected with HIV. As a result of these improvements in HIV treatment, many children now live to a young age. Therefore, neurocognitive profiles appear in HIV-infected older children and adults. Given that HIV is a chronic disease, and given the limitations of antiretroviral therapy, a significant proportion of these patients are expected to develop neurocognitive deficits and symptoms of HIV-related dementia, which is reported in the adult HIV literature.

Conclusion

In adolescents with a 3-4 clinical stage of HIV infection, damage to the nervous system in the form of HIV-associated neurocognitive disorder is manifested by a decrease in intelligence, various forms of aggressive behavior and is associated with a decrease in the quality of life in terms of physical, emotional, social activity and learning at school. To assess the severity of these disorders, method of neuro-psychological testing using the Raven matrix scale, the Bass-Darki emotion test modified by Rezapkina and the PedsQL-4 questionnaire are accessible and diagnostically informative.

Study Limitations: The amount of participant in the control group was less than that of main group to compare. It might have affect some of our results. Thus, further researches can be conducted with same amount of participants in each arm.

Acknowledgements: We are grateful to the staff of Department of Neurology, Pediatric Neurology and Medical Genetics, Department of Faculty Internal Medicine, Professional Pathology, Hospital of Internal Diseases and Propaedeutics of Internal Diseases, Department of Epidemiology, Infectious Diseases of Tashkent Pediatric Medical Institute for the cooperation in our research. The parents of the participants kindly gave full written permission for this report.

Ethical Approval: The ethical approval for the study was granted by the Committee of Ethical Approval for Researches under the Ministry of Health of the Republic of Uzbekistan.

Consent: Written informed consent was obtained from all participants' parents of the research for publication of this paper and any accompanying information related to this study. A copy of the written consent is available for review by the authors.

Conflict of Interest: The authors declare that they have no competing interests.

Funding: No funding sources to declare.

References

1. UNAIDS. Together we will end AIDS. 2012;: p. 1-140.
2. Donald KA WKKTea. HIV Encephalopathy: pediatric case series description and insights from the clinic coalface. AIDS Res Ther. 2015; 12(1)(2).
3. Foster CJ BRMDea. Neurodevelopmental outcomes in children with HIV infection under 3 years of age. Dev Med Child Neurol. 2006; 48: p. 677-682.
4. Van Rie A HPDARK. Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective. Eur J Paediatr Neurol. 2007; 11(1): p. 1–9.
5. Saidhodzhaeva SN. NS,aAU. Damage to the

nervous system in HIV infection" Medicine: Theory and Practice. 2019; 4(S): p. 488-488.

6. Van Rie A MADA. Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa. Dem-ocratic Republic of the Congo. 2008; 122: p. 123-128.
7. Chiriboga CA FSCSea. Incidence and prevalence of HIV encephalopathy in children with HIV infection receiving highly active anti-retroviral therapy (HAART). J Pediatr. 2005; 146: p. 402-407.
8. Tardieu M LCJPAea. "HIV-1-related encephalopathy in infants compared with children and adults. French Pediatric HIV Infection Study and the SEROCO Group". Neurology. 2000; 54: p. 1089-1095.
9. Van Rie A HPDAea. "Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: A global perspective". Eur J Paediatr Neurol. 2007; 11: p. 1-9.
10. A K. "Early immune activation predicts central nervous system disease in HIV-infected infants: Implications for early treatment". Clin Infect Dis. 2009; 48: p. 347-349.
11. Govender R EBWKea. "Neurologic and neurobehavioral sequelae in children with human immunodeficiency virus (HIV-1) infection". J Child Neurol. 2011; 26: p. 1355-1364.
12. Mellins CA BCEDCea. "Psychiatric disorders in youth with perinatally acquired human immunodeficiency virus infection". Pediatr Infect Dis J. 2006; 25: p. 432-437.
13. Wood SM SSSAea. "The impact of AIDS diagnoses on long-term neurocognitive and psychiatric outcomes of surviving adolescents with perinatally acquired HIV". AIDS. 2000; 23: p. 1859-1865..
14. Musisi S KE. "Emotional and behavioural disorders in HIV seropositive adolescents in urban Uganda. East Afr Med J. 2009; 86: p. 16-24..
15. Kramer-Hämmerle S RIWHea. Cells of the central nervous system as targets and reservoirs of the human immunodefi-ciency virus. Virus Res. 2005; 111: p. 194-213.
16. Banks WA ENPT. "The blood-brain barrier in neuroAIDS". Curr HIV Res. 2006; 4: p. 259-266.
17. Pearson DA MNNMea. "Predicting HIV disease progression in children using measures of neuropsychological and neurological functioning". Pediatric AIDS clinical trials 152 study team. Pediatrics. 2000; 106: p. 76.
18. Le Doaré K BRNM. "Neurodevelopment in children born to HIV-infected mothers by infection and treatment status". Pediatrics. 2012; 130: p. 1326-1344.
19. Abubakar A VBAVdVFea. "Paediatric HIV and neurodevelopment in sub-Saharan Africa: A systematic review". Trop Med Int Health. 2008; 13: p. 880-887.
20. Van Rie A MADA. "Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa". Dem-ocratic Republic of the Congo. Pediatrics. 2008; 122: p. 123-128.
21. Hoare J FJSBea. A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve "slow progressors". J Neurovirol. 2012; 18: p. 205-212.
22. Ruel TD BMBHea. "Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4 cell counts". Clin Infect Dis. 2012; 54: p. 1001-1009.
23. EJ. W. "Neurocognitive outcomes in pediatric HIV". Ment Retard Dev Disabil Res Rev. 2006; 12: p. 223-228.
24. Antinori A AGBJea. "Updated research nosology for HIV-associated neurocognitive disorders". Neurology. 2007; 69: p. 1789-1799.