The Effects of Stage of Disease, CD4 Percentages, Medication and Child-to-Adult Ratio on Cognitive Functioning in Children Infected with HIV/AIDS on Antiretroviral Treatment in South-Africa

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A.C. Spoormans, *Department of Developmental Psychology, Utrecht University, Utrecht, the Netherlands*

Supervisor: Prof. M.A.G. van Aken, PhD
General co-ordinator of the research project: Prof. A. Vermeer, PhD
Local supervisor: Sr. Alison Munro, OP

Abstract

With an estimated 5.7 million people living with HIV, South Africa is the country with the largest number of infections in the world. Patients with HIV/AIDS can be treated with Highly Active Antiretroviral Therapy (HAART). The introduction of HAART has led to a reduction in mortality. This study is done on behalf of the AIDS office of the Southern African Catholic Bishops' Conference that provides ARV (antiretroviral) medication necessary for HAART. This study concerns children with HIV/AIDS who are on ARV medication. The purpose of the current study is to examine the effect of different factors such as stage of disease, CD4 percentages, kind of medication and child-to-adult ratio on cognitive functioning. Previous studies indicate that stage of disease, as well as child-to-adult ratio, are significantly related to cognitive functioning in children infected with HIV/AIDS. Because CD4 percentage is more closely associated with cognitive performance than stage of disease, the CD4 percentages were also analysed in this study. The relationship between different kind of ARV medication and cognitive functioning has not yet been investigated. The current study involved 81 children (age 6-16) who are infected with HIV/AIDS. The Raven CPM was used to assess cognitive functioning. Also, questions about demographic facts and the child-to-adult ratio were asked. To obtain medical information concerning the children (stage of disease, CD4 percentage and medication) the medical files of the children were consulted. It was expected that all factors are significantly related to cognitive functioning. The results did not confirm this expectation. No significant effects were found of these factors on cognitive functioning. Even after controlling for the effect of age, still no significant relationship was found. In conclusion, these findings document no substantial relationship between stage of disease, kind of medication, CD4 percentages and child-to-adult ratio on the one hand and cognitive functioning of HIV/AIDS-infected children on the other.

Keywords: HIV/AIDS; South Africa; Cognitive development; Children

HIV/AIDS

About 33 million people in the world are now living with HIV (Human Immunodeficiency Virus), of whom more than 30 million live in low- and middle-income countries. Approximately 2.7 million people became newly infected with HIV, while approximately 2 million people died of AIDS-related illnesses in 2007 (UNAIDS/WHO, 2007). The scale and trends of the HIV/AIDS epidemics in the sub-Saharan region vary considerably, with southern Africa most affected. In 2007, this sub-region accounted for almost a third (32 percent) of all new HIV infections and AIDS-related deaths globally, with national adult HIV prevalence exceeding 15 percent in eight countries in 2005 (Botswana, Lesotho, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe). Nowhere else has national adult HIV prevalence reached such levels. However, there is evidence of slight declines in the epidemics of some countries (notably Zimbabwe), while the epidemics in most of the rest of the sub-region have either reached or are approaching a plateau (UNAIDS/WHO, 2008). With an estimated 5.7 million [4.9-6.6 million] people living with HIV, South Africa is the country with the largest number of infections in the world. The WHO estimates that 280,000 children (0-14 years) were living with HIV in 2007. Another consequence of AIDS is the growing number of orphans; in 2007 there were 1.4 million orphans living in South Africa (UNAIDS/WHO, 2008). More than half (55 percent) of all South Africans infected with HIV reside in the KwaZulu-Natal and Gauteng provinces (Dorrington, Johnson, Bradshaw & Daniel, 2006).

AIDS stands for Acquired Immune Deficiency Syndrome. This is a collection of symptoms that are the result of a damaged immune system caused by HIV, the Human Immunodeficiency Virus. Patients are first infected with HIV and after several years, depending on the treatment that is provided, the HIV status will shift towards the AIDS status.

HIV infection knows three stages, namely the primary HIV infection, the clinically asymptomatic stage and the early symptomatic HIV infection. The period of time before a patient reaches the AIDS status can last for an average of ten years. At first the virus can be characterized by symptoms similar to that of the flu, but sometimes people don't have any symptoms at all. After this period all patients go

through an asymptomatic period, which can last for over ten years. During this period many patients don't even notice that they are infected with HIV. Nevertheless the virus is rapidly multiplying inside the body. The T-cells are taken over by the HIV virus and as a result make new viruses. Eventually the T-cells die and the immune system gets slowly damaged. The effect of HIV can be measured by the amount of CD4+T cells in the blood. This level will decrease as time goes by. At a certain point the immune system is so badly damaged that there will be all sorts of complications. For many people the first clue for knowing that they are infected with the HIV virus is a swelling of the glands for a period of three months. Other symptoms in the years before AIDS develops are for example loss of weight and loss of short term memory.

The patient goes from having an HIV infection to having AIDS when the advanced stage of the HIV infection starts. This is determined by the following criteria: the person has less than 200 CD4+T cells in his blood and must suffer from at least 1 of 26 clinical diseases, most of which are opportunistic infections that would have been harmless in case of a normal immune system. Eventually the person can die as a result of these clinical diseases. This happens after a long period of illness. There are also HIV-infected people who never develop AIDS. How this is possible is still unknown at this time (Van Driel, 2006). However, antiretroviral drugs can slow down the process for an HIV-infected person to develop AIDS (UNAIDS/WHO, 2008).

Standard antiretroviral therapy (ART) consists of the use of at least three antiretroviral (ARV) drugs to maximally suppress the HIV virus and stop the progression of HIV disease. The estimated number of South African people (both sexes) receiving ARV medication is 460,000 in 2007, whereas an estimated 1.7 million people need this medication. Huge reductions have been seen in rates of death and suffering when a potent ARV regimen is followed (UNAIDS/WHO, 2008). When ARVs are taken regularly and with proper nutrition the rate of death can be reduced by 86 percent (Sterne, Hernan, Ledergerber, Tilling, Weber, Sendi, Rickenback, Robins, Egger & the Swiss HIV Cohort Study, 2005). It is of the utmost importance that children are diagnosed in an early stage and provided with antiretroviral therapy (ART) as soon as possible, as the course of HIV infection is faster and more aggressive in children. Many of the obstacles associated with treatment of HIV in pediatrics have to do with a lack of simple and affordable diagnostic technologies and insufficient understanding of the life-saving effects of ART in children (WHO, 2006).

In the past five years, there has been a growing interest in investigating the long-term effects of HIV infection on school-age children. School-age children represent an important group because, with improvements in antiretroviral therapy, children are living longer and healthier lives (Blanchette, Smith, King, Fernandes-Penney & Read, 2002).

Cognitive functioning

Cognitive functioning refers to a person's thinking, memory and reasoning abilities, and impairment in cognitive functioning impacts directly on a person's daily living and functioning. HIV disease and AIDS have a detrimental impact on cognitive functioning (Revicki, Chan & Gevirtz, 1998). According to the study of Nozyce *et al*., HIV-infected children have significantly more cognitive and neurodevelopmental impairments than children in the general population (Nozyce, Lee, Wiznia, Nachman, Mofenson, Smith, Yogev, McIntosh, Stanley & Pelton, 2006). Pre-HAART studies of school-age children with HIV disease typically reported mean scores of global cognitive tests in the average to low average range, with a subset of children presenting with severe neurocognitive impairments as well as neurological and neuroimaging abnormalities (Martin, Wolters, Toledo-Tamula, Zeichner, Hazra & Civitello, 2006). Papola *et al*. reported that, of a group of ninety school-age children presumed to have vertically transmitted HIV infection, 56 percent were functioning at a borderline or lower level of intelligence (Papola, Alvarez & Cohen, 1994). These findings could be explained by the influence of several factors on cognitive functioning. The present study will investigate if stage of disease, CD4 percentages, medication and child-to-adult ratio have an effect on cognitive functioning of children infected with HIV/AIDS.

Stages of the disease and cognitive functioning

The stage of disease progression, often measured in terms of immune functioning and viral burden (CD4 percentage, CD4 count), has been found to be significantly related to cognitive functioning in children with HIV (Kullgren, Morris, Bachanas & Jones, 2004). In 1990, the World Health Organization (WHO) developed a staging system for HIV disease based on clinical symptoms, which may be used to guide medical decision making. Most of these conditions are opportunistic infections that are easily

treatable in healthy people. The current staging system for HIV infection in children was developed in 2005 (WHO, 2007).

- Stage I: HIV infection is asymptomatic with persistent generalized lymphadenopathy
- Stage II: includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections
- Stage III: includes unexplained chronic diarrhea or fever, severe bacterial infections and pulmonary tuberculosis
- Stage IV: includes pneumocystis pneumonia, recurrent severe presumed bacterial infections, chronic herpes simplex infection, extra pulmonary tuberculosis and Kaposi's sarcoma; these diseases are indicators of AIDS.

The consequences of HIV-disease progression are decreases in the patient's cognitive functioning, health status and well-being. Generally, it has been shown that performance on neurocognitive tests decreases over time as a consequence of HIV-disease progression (Revicki *et al*., 1998). Studies involving infants and young children have shown that cognitive functioning often declines as the disease progresses (Frank & Foley, 1997). A recent meta-analysis of 41 studies of neuropsychological functioning in HIV-1 infection examined cognitive decline with respect to disease progression across the stages from asymptomatic to symptomatic to AIDS. From this meta-analysis it appears that small effects were revealed in the asymptomatic participants, small to moderate effects in the symptomatic participants, and moderate to large effects in cognitive decline in participants with AIDS (Baldewicz, Leserman, Silva, Petitto, Golden, Perkins, Barroso & Evans, 2004).

CD4 percentages and cognitive functioning

Because CD4 count is more closely associated with cognitive performance than stage of disease (Grassi, Perin, Borella & Mangoni, 1999), the CD4 percentages were also analysed in this study. Some studies reported no relationship between CD4 cell count and neuropsychological performance. Blanchette *et al*. (2002) found no significant association between absolute CD4 counts and performance in any area of neuropsychological functioning. Also, Boccellari and colleagues (1993) observed no relationship between cognitive performance and CD4 count (Boccellari, Dilley, Chambers, Yingling, Tauber, Moss & Osmond, 1993). However, others found that

individuals with CD4 cell counts of less than 200/mm³ were more impaired on the variety of neuropsychological measures when compared with individuals with CD4 cell counts higher than 200/mm³ (Salawu, Bwala, Wakil, Bani, Bukbuk & Kida, 2008).

Medication and cognitive functioning

Cognitive deficits are not uncommon after receiving different kinds of medication. For example, Minisini and colleagues discuss in their review the effect of systemic anticancer treatment on cognitive functioning. Unlike other reviews that have focused on breast cancer, these authors provide a thorough overview of the published work across different tumor types, including breast, lung, prostate, and ovarian carcinoma. In addition, rather than focusing exclusively on chemotherapy, the authors also review other systemic therapies, including endocrine and androgen therapy, biological response modifiers, and molecularly targeted therapies. The authors appropriately discuss the limitations of the published work, but conclude that there is sufficient evidence to support the hypothesis that systemic cancer treatments can have a detrimental effect on cognitive functioning in cancer survivors (Minisini, Atalay & Bottomley, 2004). A conclusion similar to that published in a meta-analysis by Anderson-Hanley and colleagues (Anderson-Hanley, Sherman & Riggs, 2003). The breadth of the review is a major strength by showing that cognitive problems secondary to cancer treatment are not restricted to survivors of breast cancer who have been treated with adjuvant chemotherapy. Indeed, systemic treatments for patients with lymphoma, lung, prostate, or ovarian cancer have also been reported to cause long-term cognitive problems (Ahles, 2004).

The above indicates that medication influences the cognitive functioning in people with all sorts of cancer. According to Revicki *et al*. (1998), new medical treatments for HIV disease may also impact on the deterioration in cognitive functioning because of an effect on the disease progression or treatment-related toxicities. However, the relationship between cognitive functioning and different kinds of medication (ARV's) is not yet investigated thoroughly.

The antiretroviral drugs are divided into two lines of regimen. The first-line regimen is used for naïve patients (patients who have never been exposed to ARVs before). Most HIV/AIDS patients eventually need to switch to second-line treatment because of side-effects and drug resistance. The preferred option when choosing a

first-line regimen for infants and children is two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTIs). The use of three ARV medications is currently the standard treatment for HIV infection in order to achieve the best possible suppression of viral replication and to arrest the progression of HIV disease. It is important to maximize the durability and efficacy of any first-line regimen by incorporating approaches to support adherence (WHO, 2006).

Child-to-adult ratio and cognitive functioning

The quality of the home environment is related to cognitive development as are such factors as the social class of the families and the number of children in the home (Gottfried, 1984). Current environmental factors could have additional predictive utility beyond illness factors in predicting children's cognitive performance, such that children living in homes with many children and few adults would exhibit poorer functioning in this area. A lower child-to-adult ratio in their home situation was a significant predictor of better IQ performance, such that children living in homes with fewer children per adult have better global cognitive functioning (Kullgren *et al*., 2004). Severe lack of stimulation, as experienced by children in orphanages and children living in homes with a high child-to-adult ratio, was shown to lead to lower IQ scores (Wells, 2000). The present study will investigate if there is a difference in cognitive functioning between HIV/AIDS-infected children living in homes with a low child-to-adult ratio and HIV/AIDS-infected children in homes with a high child-to-adult ratio.

Research questions

The aim of this study is to research the effect of stage of disease, CD4 percentages, medication and child-to-adult ratio on cognitive functioning of children infected with HIV/AIDS. The research questions of the current study are as follows:

1) Is there a difference in cognitive functioning between children who are in the early stage of disease and children who are in a later stage of disease?
2) Is there a difference in cognitive functioning between children with different CD4 percentages?
3) Is there a difference in cognitive functioning between children who receive different kinds of medication?

4) Is there a difference in cognitive functioning between children living in homes with a low child-to-adult ratio and children living in homes with a high child-to-adult ratio?

Methods

Subjects

The sample consists of 81 children, age 6-16 year. The mean age of this group is 9.8 years, with a standard deviation of 2.53. Among these children 40 are female en 41 are male. The children are all infected with HIV/AIDS. Most of the children are in stage 2 of the disease (N=33), a few children are in stage 4 (N=5). Stage 1 consists of 21 children and stage 3 consists of 16 children. All children are enrolled in antiretroviral treatment programmes (ARV). The antiretroviral medication is provided by the AIDS Office of the Southern African Catholic Bishops' Conference (SACBC). Most of the children receive Regimen 1A (N=54), a few children receive Bactrim (N=4. Eleven children receive Regimen 1C and eight children receive Regimen 2N. Table 1 shows the frequencies regarding medication and stage of disease.

Table 1: Frequencies of the research sample

Medication	**N**	**Mean age**	**Stage of disease**	**N**	**Mean age**
Regimen 1A	54	9.8	Stage 1	21	9.2
Regimen 1C	11	10.1	Stage 2	33	9.5
Regimen 2N	8	9.1	Stage 3	16	10.3
Bactrim	4	10.5	Stage 4	5	11
Total	77			75	

The children are recruited from different sites (community centres, orphanages and clinics) in South Africa, located in the provinces of Gauteng and KwaZulu Natal.

Instruments

In this study the Raven (1938) Coloured Progressive Matrices (CPM) is used. The CPM can be used to assess the degree to which people can think clearly and make sense of complexity. The Raven is a multiple choice test that consists of 36 items in three sets (A, Ab and B) with twelve items per set. The first three items of set A are tasks for practicing, so there are no correct or wrong answers. These automatically score the correct answer. The three sets together provide three opportunities for a person to develop a consistent theme of thought, and the scale of 36 problems as a whole is designed to assess, as accurately as possible, mental development up to intellectual maturity (Raven, 1995).

The items are arranged to assess mental development up to the stage when a person is sufficiently able to reason by analogy to adapt this way of thinking as a consistent method of inference. Also, the items are presented on a coloured background to make the test visually stimulating for the children. The test can be demonstrated to children of almost any race and speaking any language (Raven, 1995). A child is asked to look for the missing piece that is required to complete the larger pattern. For his answers, the child could choose from six alternatives.

The Raven CPM has an internal consistency reliability of .88 (Raven, 1995). The split-half reliability estimate of .90 was reported, with no differences by ethnicity or sex. Various cultural contexts, including Africa, India and Asia have yielded validity data typically around .6 to .7, with authors emphasizing the significance of cultural backgrounds in evaluating results (Raven, 1995).

Also, the child was asked demographic questions and one question about the child-to-adult ratio at home. This last question was presented as follows: "With how many children are you living at home and with how many adults?"

A MINDS (Mental Information processing and Neuropsychological Diagnostic System) programme was used to run the Raven CPM on a laptop. MINDS is a package that allows psychological tests and questionnaires to be assessed and scored. The obtained test results can be textual and numerical, as well as graphical, processed into a file or record. Also, the data can be exported into a SPSS-syntax file (Statistical Package for the Social Sciences) (Brand, 2008).

Procedure

The children were recruited at different ARV-providing sites in two provinces of South Africa (Gauteng and KwaZulu Natal). The different sites were established by the AIDS Office staff members of the SACBC. The researchers contacted and visited the sites. At every site one of the staff members selected the children who were to participate in the study. The research took place at different settings. These settings were orphanages, ARV-clinics and community centres.

First, the child was asked questions about demographic facts and the child-to-adult ratio. Then the Raven CPM was executed to test the cognitive abilities of the children. A MINDS programme was carried out to run the Raven CPM on a laptop. The researchers both assessed one child at a time. The purpose of the test was

explained in English. When the child did not speak or understand English, a caregiver accompanied the researchers to translate.

To obtain medical information concerning the children (stage of disease, CD4 percentage and medication) the medical files of the children were consulted. For medication, there are different combinations possible. The children receive three ARV medications, two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTIs) (see table 2). Some children do not yet receive ARV-treatment, they receive Bactrim. Bactrim (trimethoprim and sulfamethoxazole) is used in the treatment of a variety of bacterial infections.

Table 2: Different regimens of ARV medications

	NRTI		**NRTI**		**NNRTI**	
Regimen 1A	Stavudine		Lamivudine		Efavirenz	
Regimen 1C	Zidovudine		Lamivudine		Efavirenz	
Regimen 2N	Non-specific					

Design and analyses

The design of the research questions is a within-subject design. The dependent variable of the research questions is cognitive functioning. The stage of disease, CD4 percentages, medication and child-to-adult ratio are the independent variables in the research questions. The covariate is age.

The statistical analyses regarding cognitive functioning will be obtained by using the computer program SPSS 15.0. To test differences in cognitive functioning between children who are in different stages of disease, an ANOVA test was used. A correlation test (Pearson) was used to test the association between cognitive functioning and different CD4 percentages. Regarding research question 3, an ANOVA test was used to test the difference in cognitive functioning between children who received different kinds of medication. Because some groups consisted of very few children (N≤5), the data were recoded. Regimen 1B, regimen 2N and 'bactrim' were put together into the group 'regimen 2 non-specific' (2N). A correlation test (Pearson) was used to establish the association between cognitive functioning and child-to-adult ratio. Also, with respect to child-to-adult ratio, two groups were formed, namely, a low child-to-adult ratio group and a high child-to-adult ratio group. A low child-to-adult ratio ranged from 0 to 4 children per adult, a high child-to-adult ratio

ranged from 5 to 9 children per adult. Subsequently, an ANOVA test was used to look again at the difference in cognitive development between children with a low or a high child-to-adult ratio.

Because of a difference in age between the groups, an ANOVA test with covariate or a Partial Correlation test with covariate was established to control for the effect of age. This was done for all research questions.

Results

Stage of disease and cognitive functioning

An ANOVA test was used to establish differences in cognitive functioning between children in different stages of disease. No significant difference was found (F = .674; df = 3; p > .05). This means that the cognitive functioning of children in the four stages of disease do not significantly differ from each other (see table 3).

Table 3: Mean sum scores of children in different stages of disease; ANOVA test

		N	Mean	SD	F	Sig.
Sum scores	*Stage 1*	21	13.38	2.78	.674	.571
	Stage 2	33	14.03	4.11		
	Stage 3	16	12.88	3.50		
	Stage 4	5	15.40	7.27		

Even after controlling for the effect of age, there is still no significant difference between different stages of disease on cognitive functioning (F = .965; df= 3; p > .05).

CD4 percentages and cognitive functioning

A correlation test (Pearson) was carried out to test if there is an association between cognitive functioning and different CD4 percentages. No significant correlation was found (r = -.100; p = .389). Even after controlling for the effect of age, there is still no significant difference between different CD4 percentages on cognitive functioning (Partial r = .011; p > .05).

Medication and cognitive functioning

To assess the difference in cognitive functioning between children who receive different kinds of medication an ANOVA test has been completed. The results show no significant difference in cognitive functioning between children who receive different kinds of medication (F = .644; df = 2; p > .05). See table 4 for details.

Table 4: Mean sum scores of children with different kinds of medication; ANOVA test

		N	Mean	SD	F	Sig.
Sum scores	*Regimen 1A*	54	13.65	4.05	.644	.528
	Regimen 1C	11	14.73	4.98		

	*Regimen 2N**	16	14.81	4.29		

* This includes Regimen 1B, Regimen 2N and Bactrim

After controlling for the effect of age the adjusted mean for regimen 1A is 13.70 (std. error .509), for regimen 1C is 14.53 (std. error 1.128) and for regimen 2N is 14.79 (std. error .935). Even after controlling for the effect of age, there is still no significant difference between different kinds of medication on cognitive functioning ($F(2,77) = .637$; $p > .05$).

Child-to-adult ratio and cognitive functioning

A correlation test (Pearson) was carried out to test if there is an association between cognitive functioning and different child-to-adult ratios. No significant correlation was found ($r = -.027$; $p > .05$). Even after controlling for the effect of age, there is still no significant difference in cognitive functioning related to child-to-adult ratio (Partial $r = .017$; $p > .05$). Subsequently, an ANOVA test was used to look again at the difference in cognitive development between children with a low or a high child-to-adult ratio. There was no significant difference between children with a low or high child-to-adult ratio ($F = 1.279$; $df = 1$; $p > .05$).

Discussion

Previous studies indicate that there is a significant difference in cognitive functioning between HIV/AIDS-infected children and non HIV/AIDS-infected children. In the master thesis of Van Loon the same sample population was used as in the present study. Van Loon also found a significant difference in cognitive functioning between HIV/AIDS-infected children and non-infected children (Van Loon, 2009). The aim of this study was to look at the effect of stage of disease, CD4 percentages, medication and child-to-adult ratio on cognitive functioning of children infected with HIV/AIDS.

Stage of disease and cognitive functioning

A relationship between stage of disease and cognitive functioning has been consistently reported in other studies (Kullgren *et al*., 2004; Frank & Foley, 1997; Baldewicz *et al*., 2004). Therefore, it was surprising to find that the stage of disease did not add up to the prediction of cognitive performance in this study. There was no significant difference in cognitive functioning between the HIV/AIDS-infected children at different stages of disease. This unexpected outcome can be explained by taking into account the number of children in the sub-groups (different stages of the disease) within the HIV+ group. Most of the children are in stage 2 of the disease (N=33), while only a small number of children are in stage 4 (N=5). Because of the small number of children in de stage 4 group, these children could be, by coincidence, more cognitive developed than the children in the other stages, due to a greater disposition or higher intelligence. An alternative explanation is that stage 4 children are more likely to be unable to participate in this study, making the stage 4 group not representative to the whole stage 4 group, and more or less comparable to the stage 3 group.

It is also possible that no relationship was found because of the difference in design of the studies. All studies that reported a relationship between stage of disease and cognitive functioning, are longitudinal and within-subjects studies. Children who are moving from one stage to another, are being followed individually for several years. Therefore, these studies pronounce upon the cognitive functioning of individuals over time. However, the current study was a between-subjects study. In this, the four groups were compared at one moment in time, no second measurement took place.

Finally, it was also not always clear what stage of disease the child was in. In many times documentation in the medical files was very poor, so the researchers had to rely on the caregivers' opinion to determine what stage of disease the child was in. Often the researchers got the impression that the caregiver was just guessing. This fact may have disturbed the results of the current study.

CD4 percentages and cognitive functioning

No significant association was found between cognitive functioning and different CD4 percentages. This can be explained by the fact that the immunologic data (CD4 percentages) differ according to the time of measurement, due to different medical monitoring programmes at the sites. For some children the CD4 count was done a few years ago, while for other children the CD4 count was more up-to-date. This fact may also have influenced the results of the current study.

Another explanation is that the CD4 count may be a poor indicator of neurocognitive status in HIV/AIDS-infected children. Blanchette *et al*. (2002) and Boccellari *et al*. (1993) also did not find a significant association between CD4 count and performance in any area of neuropsychological functioning. It could be that there simply is no relationship between cognitive functioning and CD4 count. This could explain why the current study did not find a significant association between cognitive functioning and different CD4 percentages.

Medication and cognitive functioning

Our results indicate that cognitive functioning is not related to the different kind of medication. According to Revicki *et al*. (1998) new medical treatments for HIV disease may have an impact on the deterioration in cognitive functioning because of the effect on the disease progression or treatment-related toxicities. However, this is an assumption and the relationship between cognitive functioning and different kinds of medication was never investigated. Again, it could be that there just is no relationship between cognitive functioning and different kinds of medication. This could explain why the present study did not find a significant difference between cognitive functioning and different kinds of medication.

Child-to-adult ratio and cognitive functioning

A relationship between child-to-adult ratio and cognitive functioning has been reported in several studies (Kullgren *et al*., 2004; Wells, 2000). Severe lack of stimulation, as experienced by children in orphanages and children living in homes with a high child-to-adult ratio, was shown to lead to lower IQ scores. Contrary to our expectations, no significant relationship was found between cognitive functioning and child-to-adult ratio in the current study. A possible explanation is that the quality of child care in the orphanages has improved and that caregivers pay more attention to and provide greater stimulation of cognitive functioning.

Limitations

As in every research, limitations should be noted. Limitations of the present study include difficulties in examining covariation of variables such as maternal drug and/or alcohol abuse, neurological status, parental separation and death, changes of caregivers, nutrition, poverty and low social economic status. All of these factors have a huge impact on cognitive functioning, especially maternal drug abuse (Blanchette *et al*., 2002). It has been estimated that 57 percent of the children with HIV/AIDS are born of drug-addicted mothers. This variable is an important consideration when investigating cognitive development in children because children perinatally exposed to a number of drugs are at risk for developmental delay. As a consequence, it has been extremely difficult for studies to separate the effects of HIV disease and in utero drug exposure (Levenson, Mellins, Zawadzki, Kairam, Stein, 1992). It has been difficult to identify pediatric samples large enough to allow for systematic control of these confounding factors. For example, the caregivers of children infected with HIV frequently are not the biological parents, so information on the child's past is often unreliable or unknown.

In South Africa, eleven official languages are used. At most visited sites the language being used generally was English. When possible the Raven CPM was administered by testers who spoke English to the child, but often it was necessary to make use of a translator during testing. The translators ranged from caregiver to grandmother. Sometimes the researchers got the impression that the translators tried to help the children with the tasks. It is well-known that when a task is translated, the reliability and validity of the results may be weakened, resulting in different rates of

outcomes (Smith, Malee, Leighty, Brouwers, Mellins, Hittelman, Chase & Blasini, 2006).

The above mentioned potential limitations may impact the interpretation and generalization of these results. Generalization may be compromised because the children in this study, although representative of perinatally infected children and not infected children in rural South Africa, may differ in important ways from other populations of children infected with HIV such as children infected with HIV/AIDS from western countries.

Besides these limitations, the current study also has many strong points. The test used in this study is a standardized intelligence test. The advantage of using a standardized test is that the test can eliminate biases in assessments of individual children. Goodwin and Driscoll (1980) note that standardized tests have the following qualities: they provide a systematic procedure for describing behaviors, they include specified procedures for administration and scoring, the test items are derived from experience rather than theory, they have an established format and set of materials and they present the same tasks and require the same response modes from all test takers. All of these qualities can be applied to the Raven CPM. Also, a MINDS program was used to score the results of the Raven CPM and to export these results into a SPSS-syntax file. Due to this, the possibility of making mistakes is reduced.

Another advantage of this study is that the Raven CPM was assessed individually and not in groups. In comparison to children assessed individually, children assessed in a group setting will pay less attention to the assessment task, be less comfortable and experience more disruptive behavior in the assessment situation (Atkinds-Burnett, Rowan & Correnti, 2001). The results of the current study are not biased by these factors.

With advances in research and clinical practice, pediatric HIV infection is changing from a terminal disease to a chronic illness with children living longer and healthier lives. Thus, future studies should focus on longitudinal follow-up of children with HIV infection to examine (the pattern of) the relationship between cognitive functioning and medical variables over time and to describe the developmental process and profile of this group of children. With such efforts, health professionals

will be able to provide optimal medical, educational, psychosocial and rehabilitative services to patients and their families.

A better understanding of typical development patterns would facilitate the provision of appropriate interventions for these children, such as greater stimulation at school, special education and counseling. With early, appropriate, antiretroviral therapy, not only do the odds of survival increase, but also children may be protected from significant cognitive impairment.

References

Ahles, T. A. (2004). Do Systemic Cancer Treatments Affect Cognitive Function? *The Lancet Oncology*, *5*, 270-271.

Anderson-Hanley, H. C., Sherman M. L., & Riggs R. (2003). Neuropsychological Effects of Treatments for Adults with Cancer: a Meta-analysis and Review of the Literature. *Journal of the International Neuropsychological Society*, *9*, 967-982.

Atkinds-Burnett, S., Rowan B., & Correnti, R. (2001). Administering standardized achievement tests to young children: how mode of administration affects the reliability and validity of standardized measures of student achievement in kindergarten and first grade. *School of education*, University of Michigan.

Baldewicz, T. T., Leserman, J., Silva, S. G., Petitto, J. M., Golden, R. N., Perkins, D. O., Barroso, J., & Evans, D. L. (2004). Changes in Neuropsychological Functioning with Progression of HIV-1 Infection: Results of an 8-Year Longitudinal Investigation. *AIDS-and-Behavior*, *8 (3)*, 345-355.

Blanchette, N., Smith, M. L., King, S., Fernandes-Penney, A., & Read, S. (2002). Cognitive Development in School-Age Children with Vertically Transmitted HIV Infection. *Developmental Neuropsychology, 21 (3)*, 223-241.

Boccellari, A. A., Dilley, J. W., Chambers, D. B., Yingling, C. D., Tauber, M. A., Moss, A. R., & Osmond, D. H. (1993). Immune Function and Neuropsychological Performance in HIV-1-Infected Homosexual Men. *Journal of Acquired Immune Deficiency Syndromes*, *6 (6)*, 592-601.

Brand, N. (2008). *Handleiding MINDS Versie 1.2* Utrecht University, bureau MindsWare.

Coscia, J. M., Christensen, B. K., Henry, R. R., Wallston, K., Radcliffe, J., & Rutstein, R. (2001). Effects of Home Environment, Socioeconomic Status, and Health Status on Cognitive Functioning in Children With HIV-1 Infection. *Journal of Pediatric Psychology*, *26 (6)*, 321-329.

Dorrington, R. E., Johnson, L. F., Bradshaw, D., & Daniel, T. (2006). *The Demographic Impact of HIV/AIDS in South Africa: National and Provincial Indicators for 2006.* Cape Town, Centre for Actuarial Research, South African Medical Research Council and Actuarial Society of South Africa.

Frank, E. G., & Foley, G. M. (1997). Cognitive Functioning in School-Age Children with Human Immunodeficiency Virus. *Perceptual and Motor Skills*, *85*, 267-272.

Gottfried, A. W. (1984). *Home Environment and Early Cognitive Development: Longitudinal Research*. Academic Press, New York.

Goodwin, W. L., & Driscoll, L. A. (1980). *Handbook for measurement and evaluation in early childhood education*. San Francisco: Jossey-Bass.

Grassi, M. P., Perin, C., Borella, M., & Mangoni, A. (1999). Assessment of Cognitive Function in Asymptomatic HIV-Positive Subjects. *European Neurology*, *42*, 225-229.

Joint United Nations Programme on HIV/AIDS (UNAIDS) (2006). *Report on the Global AIDS Epidemic*. Geneva: UNAIDS.

Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) (2008). *Sub-Saharan Africa AIDS Epidemic Update Regional Summary*. Geneva: UNAIDS.

Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) (2007). *Global Summery of the AIDS Epidemic*. Geneva: UNAIDS.

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

Martin, S. C., Wolters, P. L., Toledo-Tamula, M., Zeichner, S. L., Hazra, R., & Civitello, L. (2006). Cognitive Functioning in School-Aged Children with Vertically Acquired HIV Infection Being Treated With Highly Active Antiretroviral Therapy (HAART). *Developmental Neuropsychology*, *30*, 633-657.

Minisini, A. M., Atalay G., & Bottomley, A. (2004). What is the Impact of Systemic Anticancer Treatments on Cognitive Functioning? *Lancet Oncology*, *5*, 273-282.

Nozyce, M. L., Lee, S. S., Wiznia, A., Nachman, S., Mofenson, L. M., Smith, M. E., Yogev, R., McIntosh, K., Stanley, K., & Pelton, S. (2006). A Behavioral and Cognitive Profile of Clinically Stable HIV-Infected Children. *Pediatrics*, *117*, 763-770.

Papola, P., Alvarez, M., & Cohen, H. J. (1994). Developmental and Service Needs of School-Age Children with Human Immunodeficiency Virus Infection: A Descriptive Study. *Pediatrics*, *94*, 914–918.

Revicki, D. A., Chan, K., & Gevirtz, F. (1998). Discriminant Validity of the Medical Outcomes Study Cognitive Function Scale in HIV Disease Patients. *Quality of Life Research*, *7*, 551-559.

Selnes, O. A., Galai, N., Bacellar, H., Miller, E. N., Becker, J. T., Wesch, J., Van Gorp, W., & Mc Argter, J. C. (1995). Cognitive Performance after Progression to AIDS: a Longitudinal Study from the Multicenter AIDS Cohort Study. *Neurology*, *45*, 267-275.

Smith, R., Malee, K., Leighty, R., Brouwers, P., Mellins, C., Hittelman, J., Chase, C., Blasini, I. & for the Women and Infants Transmission Study Group (2006). Effects of Perinatal HIV Infection and Associated Risk Factors on Cognitive Development Among Young Children. *Pediatrics*, *117*, 851-862.

Sterne, J. A. C., Hernan, M. A., Ledergerber, B., Tilling, K., Weber, R., Sendi, P., Rickenbach, M., Robins, J. M., Egger, M., & the Swiss HIV Cohort Study (2005). Longterm effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *The Lancet*, *366*, 378-384.

Van Loon, S. E. (2009). Cognitive Functioning of Children Infected with HIV/AIDS on Antiretroviral Treatment Compared to a Control Group in South Africa. Master thesis, Department of Developmental Psychology, Utrecht University.

Wells, N. M. (2000). At Home With Nature: Effects of "Greenness" on Children's Cognitive Functioning. *Environment and Behavior*, *32*, 775-795.

World Health Organization (WHO) (2006). Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a Public Health Approach. *WHO Library Cataloguing-in-Publication Data*.

World Health Organization (WHO) (2007). Disease Staging System for HIV Infection and Disease in Children. *WHO Library Cataloguing-in-Publication Data*.