The Cognitive Functioning of Children Infected with HIV/AIDS on Antiretroviral Treatment Compared to a Control Group in South Africa

Master thesis, February 2009

S.E. van Loon (0413283), *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 medication necessary for HAART. The purpose of current study is to examine the differences in cognitive functioning between children who are infected with HIV/AIDS (HIV+) compared to children who are not infected with HIV/AIDS (HIV-). Previous studies indicate a significant lower cognitive functioning of HIV/AIDS-infected children. There were 167 children (age 6-16) involved in this study, from which 81 children in the HIV+ group, enrolled in the HAART program and 86 children in the HIV- group. The Raven CPM was used to assess cognitive functioning. The HIV+ group was expected to have lower scores on the Raven CPM than the HIV- group. The results confirmed this expectation: a significant difference was found between the two groups on cognitive functioning. Even after controlling for the effect of age, there was still a significant difference. Concluding, these findings document a significant lower cognitive functioning, measured by means of the Raven CPM, of HIV/AIDS-infected children when compared to an ethnically similar group of uninfected children.

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 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). Coscia *et al*. studied the detrimental effects of HIV/AIDS on cognitive functioning and found that cognitive deficits may be directly related to the effects of HIV on the central nervous system (CNS), or to the effects of CNS infections or neoplasms secondary to immunocomprise (Coscia, Christensen, Henry, Wallston, Radcliffe & Rutstein, 2001).

Research question

The aim of the current study is to look at the cognitive functioning of children infected with HIV/AIDS compared to a control group. The research question of the current study is as follows:

- Is there a difference in cognitive functioning between children infected with HIV/AIDS (HIV+) and children not infected with HIV/AIDS (HIV-)?

Methods

Subjects

The HIV+ group 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 (see table 1). The children of the HIV+ group are all infected with HIV/AIDS. All the 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).

The HIV- group includes 86 children in the age of 6-16 year. Of this group the mean age is 10.8, with a standard deviation of 2.64. Among them 47 are female and 39 are male (see table 1). Because there is a difference in mean age between the HIV+ group and the HIV- group, age will be considered as a covariate.

Table 1: Frequencies of the research sample

	HIV+ group		**HIV- group**		**Total**	
Total N	81		86		167	
Females	40		47		87	
Males	41		39		80	
Mean age	9.8 (sd 2.53)		10.8 (sd 2.64)		10.2 (sd 2.62)	

The children of the HIV+ group and the HIV- group 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 12 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.

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).

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 of both groups (HIV+ and HIV- group) were recruited at different ARV-providing sites in two provinces of South Africa (Gauteng and KwaZulu Natal). In most cases, the HIV- group consisted of brothers or sisters of the children of the HIV+ group. Sometimes the social workers selected HIV-negative children living in the neighborhood, if brothers or sisters were not available. 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. 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. The task of the child was to look for the missing piece that is required to complete a larger pattern. For his answers, the child could choose from six alternatives.

Design and analyses

The design of the research question is a between-subject design. The dependent variable in the main research question is cognitive development. The independent variable is the HIV/AIDS infection. The covariate is age, because there is a difference in mean age between the HIV+ group and the HIV- group.

The statistical analyses regarding cognitive functioning will be obtained by using the computer program SPSS 15.0. An independent samples T-test was used to establish the differences in cognitive functioning between the HIV+ group and the HIV- group. Because of a difference in age between the groups, an ANOVA test with covariate was used to control for the effects of age.

Differences in cognitive functioning between the HIV+ group and the HIV- group

To assess the difference in cognitive functioning between the HIV+ group and the HIV- group, an independent samples T-test has been completed. The scores of the Raven CPM are measured in sum scores of set A, Ab and B and range from 3 to 36. In total 167 children filled out the Raven CPM. Table 2 shows the sum scores in relation to the HIV+ group and the HIV- group.

Table 2: Sum scores; independent samples T-test, two tailed

		N	Mean	SD	T	Sig.
Sum scores	*HIV+ group*	81	14.02	4.21	5.010	.000
	HIV- group	86	17.97	5.78		

A significant main effect was found between the HIV+ group and the HIV- group ($t = 5.010$; $df = 165$; $p < .001$). Children who are infected with HIV/AIDS have a lower mean score (mean = 14.02) on the Raven CPM than children who are not infected with HIV/AIDS (mean = 17.97).

To establish the effect of age on the difference between the HIV+ group and the HIV- group in cognitive functioning, an ANOVA test with covariate has been completed. The covariate age has a significant effect on cognitive functioning ($F (1,164) = 75.42$; $p < .001$) and there appeared to be significant differences in cognitive functioning between the HIV+ group (M = 14.56; SD error = .473) and the HIV- group (M = 17.46; SD error = .458): $F (1,164) = 19.17$; $p < .001$. Thus, even after controlling for the effect of age, there is still a significant difference between the HIV+ group and the HIV- group on cognitive functioning.

Cognitive functioning

The aim of this study was to look at the differences in cognitive functioning between children who are infected with HIV/AIDS and children who are not infected with HIV/AIDS. This research documents a significant lower cognitive functioning, measured by means of the Raven CPM, of HIV/AIDS-infected children when compared to an ethnically similar group of uninfected children. This finding is consistent with previous studies, which also reported a significant relation between HIV/AIDS and cognitive functioning (Revicki *et al*., 1998; Martin *et al*., 1994 & Papola *et al.*, 1994).

A possible explanation is that cognitive deficits may be directly related to the effects of HIV on the central nervous system (CNS), or to the effects of CNS infections or neoplasms secondary to immunocomprise. Neuroimaging studies have demonstrated a high incidence of structural brain abnormalities in children with symptomatic HIV infection, including cortical atrophy, white matter abnormalities and calcifications, and researchers have found that children with white matter abnormalities were more impaired on measures of cognitive functioning (Coscia, Christensen, Henry, Wallston, Radcliffe & Rutstein, 2001).

Furthermore, HIV/AIDS disease could have an impact on school functioning. Symptoms related to chronic conditions may result in frequent absences (Nabors & Lehmkuhl, 2004). Missing more time at school than classmates, may cause these children to fall behind academically. Also, the disease saps energy, making it difficult to participate fully in school life (Thies, 1999). Associated weakness, fatigue, and nausea, in addition to continued experiences of chronic pain, may further impair the child’s functioning in the classroom (Nabors & Lehmkuhl, 2004). The combination of chronicity, absence, and side effects of the illness and treatment is subtle, but the cumulative effect is potentially damaging. Falling behind in school achievement leads to catching up and catching up takes time away from keeping up (Thies, 1999).

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 in 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 to separate the effects of HIV-disease and in utero drug exposure on cognitive functioning (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 we 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 circumstances of the children in this study may differ in important ways from the circumstances of other populations of children infected with HIV/AIDS, such as children in 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 will be 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.

The Raven CPM pretends to be a test that is not culturally bounded. However, in most cases the children in South Africa did not have any experience with tasks like the Raven. That is why the current study did not use norm groups as a frame of reference, but a HIV- group that is comparable to an HIV+ group on experiences with tasks like the Raven. By using a HIV- group, influencing factors like background and environmental factors are also taken into consideration.

Finally, a strong point of the current study is the large sample size. In general, the larger the sample size, the more valid are the results.

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 intensive 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*. Universiteit Utrecht, 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.

Levenson, R. L., Mellins, C. A., Zawadzki, R., Kairam, R., & Stein, M. (1992). Effects of Pediatric HIV Infection and Prenatal Drug Exposure on Mental and Psychomotor Development. *Journal of Pediatric Psychology*, *19 (5)*, 617-628.

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.

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*.