Universiteit Utrecht

Cognition in high-functioning HIV-seropositive males:

A role for cognitive reserve?

M.H.M. Ensing

First supervisor: M.J.E. van Zandvoort

Second supervisor: A. Keizer

Student number: 3518949

Date: 10-06-2016

Abstract

Background HIV is a well-known infection, affecting thousands of people on a daily basis. About 25.000 people are infected in The Netherlands, and it is most commonly spread through male-to-male intercourse. As HIV has been turned from a potential deadly disease into a chronic, manageable one, people with HIV tend to become older, facing an aging process burdened by the HIV infection. Several studies have been conducted on cognition in HIV-infected individuals, however, participants in this study were all fully participating in society, succeeded a professional education and had mentally demanding jobs. Cognition in a sample with these characteristics has never been studied before. We therefore intent to explore cognition in this high-functioning subgroup of the HIV-infected population, searching for a possible distinct cognitive profile.

Methods 29 HIV-infected males performed extensive neuropsychogical testing to examine their cognition. Domains tested were Executive functioning, Attention/Working memory, Learning/Memory and Speed. Participants were divided into an impaired or unimpaired group, in case of a single test score 2 SD's below average. Clinical and demographic characteristics were compared between the impaired and unimpaired group.

Results In the impaired group, the domain Speed was most impaired. Clinical and demographic characteristics were compared between the impaired and unimpaired group. There were no significant differences in age, years of education, duration of illness or CD4 nadir between the impaired and unimpaired group.

Conclusion When cognitive impairment was present, the domain Speed was most affected in this sample of high-functioning HIV-infected, virologically suppressed males. It remains unclear whether the present cognitive profile is due to HIV-associated acceleration of aging of the brain, or the influence of the relatively large amount of cognitive reserve of the participants. Further research is needed to study for the continuation of this distinct cognitive profile in this high-functioning subgroup of the HIV-infected population.

Keywords: HIV, Cognition, Cognitive reserve, CD 4 nadir, Duration of illness

Introduction

Human Immunodeficiency Virus, or HIV, is one of the most well-known infections around the world, affecting thousands of people on a daily basis. About 36.900.000 people around the world are HIV-seropositive; in The Netherlands 25.000 people are infected (Van der Noordt & Op de Coel, 2014). Besides being a sexually transmitted disease, HIV can also be transferred from mother to child during pregnancy or birth, and through the use of HIV-infected products (e.g. needles). In The Netherlands, HIV is most commonly spread through male-to-male sexual intercourse (Van der Noordt & Op de Coel, 2014).

The hallmark of HIV infection is the progressive reduction of CD4 cells due to both a reduced production as well as an increased destruction of cells (Cooper, García, Petrovas, Yamamoto, Koup & Nabel, 2013). CD4 cells are T-cells which assist the immune system when attacked. Untreated, HIV-infection will lead to Acquired Immuno Deficiency Syndrome (AIDS), where the amount of CD4 cells drop below a deadly level, making the individual's immune system extremely vulnerable (Maartens, Celum & Lewin, 2014).

Nowadays, HIV is well-treated by combination antiretroviral therapy regimens, which are able to suppress viral replication. This treatment turned HIV from a potential deadly disease into a chronic, manageable one. Standard antiretroviral therapy regimens combine three types of inhibitors into one (or more) tablet(s). After initiation of successful combination antiretroviral therapy, the HIV-blood levels will decrease to concentrations below limits of detection (Maartens, Celum & Lewin, 2014).

Although the potential lethality of HIV is now well-managed by drug therapy, HIV is also known for its effects on the brain. HIV enters the brain in the early stage of infection, affecting neurocognitive functioning (An, Groves, Gray, Scaravilli, 1999; Heaton et al., 2010). Several functional imaging studies showed that HIV affects specifically the fronto-striatal pathway, causing inflammations and altering its activity (Kumar, Borodowsky, Fernandez, Gonzalez, Kumar, 2007; Du Plessis, Vink, Joska, Koutsilieri, Stein & Emsley, 2014). Furthermore, since life expectancy has greatly improved (Dore, McDonald, Li, Kaldor & Brew, 2003), HIV-infected patients now become older, facing an aging process burdened by the HIV-infection. As shown by Pfefferbaum et al. (2014), the aging HIV-infected brain shows frontal-striatal damage similar to much older 'normal' aging subjects, suggesting HIV induces acceleration of aging of the brain. Since the frontalstriatal pathway is known as a key system in the executive systems (Grant, 2008; du Plessis, Vink, Joska, Koutsilieri, Stein&Emsley, 2014), cognitive impairment in the executive domain is probable. Yet most HIV-seropositive individuals show subtle and spotty cognitive impairment. Many cognitive domains can be impaired, such as

attention/working memory, speed of information processing, learning, retrieval, motor skills, and executive functioning (Carey, Woods, Rippeth, Gonzalez, Moore, Marcotte, Grant & Heaton, 2004; Durvasula, Miller, Myers & Wyatt, 2001; Singh et al., 2013). However, since executive functioning is known to be an overall controller for other cognitive abilities (Diamond, 2013), decreased functioning of the executive functions may cause an overall decline in cognitive abilities, underlying the observed spotty impairment in cognition in HIV+ individuals. This was supported by Heaton at al. (2010), who found the executive functions to be most impaired in his large cohort of HIV-infected individuals. However, participants in this cohort were on average less highly educated compared to this sample, in which all participants completed a professional education. Furthermore, one third of the participants in Heaton's study was unemployed, compared to this fully-employed sample. As the participants in this sample are all participating in society, succeeded a professional education, and all have mentally demanding jobs, they might show a different cognitive pattern compared to earlier studies. Furthermore, as there has not been a study conducted on this high-functioning subgroup of the HIV-infected population, it is important to explore cognition in this subgroup for possible differences. Therefore, the first aim of this study is to explore cognition in HIV-seropositive males with high education and mentally demanding jobs, which are fully participating in society.

The second aim is to examine whether years of HIV-infection and CD4 nadir levels affect cognition. CD4 nadir is the lowest level of CD4 cells measured in participants' blood. As mentioned before, HIV might induce acceleration of aging of the brain (Cohen et al., 2015; Pfefferbaum, 2014). Therefore, the duration of the illness might also affect cognition. Also, CD4 nadir levels have shown to be a predictor of cognitive impairment, where low levels of CD4 nadir made participants at higher risk of developing cognitive impairment (Ellis et al., 2011). We therefore intent to explore whether CD4 nadir levels and the amount of time participants have been HIV+ affect cognition.

Methods

Participants

Participants were male virologically suppressed HIV-infected patients (N=29), aged 27-50 years, currently on combination antiretroviral (cART) consisting of only EFV/FTC/TDF STR (Atripla®). Participants were included when HIV-1 RNA was <50 copies/ml. Participants were excluded in case of hepatitis C-infection; insufficient knowledge of the Dutch language; any psychiatric disorders classified according to the DSM IV; and any neurological diseases. Participants experienced no cognitive dysfunction in daily life.

Task and Stimuli

The comprehensive 80-minute neuropsychological battery was compromised of the following measures, as shown in table 1: Controlled Oral Word Association Test (DAT) (Schmand, Groenink, & Van den Dungen, 2008); Category fluency (animals) (Van der Elst, Van Boxtel, Van Breukelen & Jolles, 2006); Trail Making Test, Parts A and B (Reitan & Wolfson, 1985); Brixton Spatial Anticipation Test (Burgess & Shallice, 1997); Visual Elevator (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994); Digit Symbol, Symbol Search, and the Letter-Number-Sequencing, from the Wechsler Adult Intelligence Scale – Fourth Edition NL (Wechsler, 2013); Rey Auditory Verbal Learning Test (Rey, 1941); Rey Complex Figure Test (Rey, 1941); Paced Auditory Serial Addition Test (Gronwall & Sampson, 1974); Grooved Pegboard (Roy, & Square-Storer, 1994). All participants conducted the above-mentioned tests, according to the manufacturer's instructions.

Table 1. Neuropsychological test battery arranged by the four major ability areas

Executive functioning	**Learning& Memory**
Controlled Oral Word Association Test – DAT	Rey Auditory Verbal Learning Test
Category fluency – Animals	Rey Auditory Verbal Learning Test recall
Brixton Spatial Anticipation Test	Rey Complex Figure Test recall
Strategy Rey Complex Figure	
Rey Complex Figure Test copy	
Attention/ Working memory	**Speed of information processing & Motor speed**
Trail making Test Part B	Digit Symbol WAIS-IV NL
Visual Elevator	Symbol Search WAIS-IV NL
Paced Auditory Serial Addition Test	Trail making Test Part A
WAIS-IV NL LNS	Grooved Pegboard Time (dominant)
	Grooved Pegboard Time (non-dominant)

Procedure

After being screened for in- and exclusion criteria, participants signed an informed consent form. HIV-RNA levels and CD4 cell count were checked through blood samples. Secondly, participants received questionnaires, as part of the ESCAPE trial protocol. At last, participants started the neuropsychological testing, which took place at the Infectious Disease department at the UMC Utrecht.

Participants conducted the test-battery in the following order; Digit symbol, RAVL test, Rey Complex Figure, Brixton Spatial Anticipation Test, Symbol Search, TMT A&B, Grooved Pegboard, Visual Elevator, delayed recall RAVL, delayed recall Rey Complex Figure, COWAT – DAT, Category Fluency animals, Letter-Digit Substitution Test and at last the PASAT. Instructions were explained verbally by the examiner, according to the manuals of the tests. When drawing the Rey Complex Figure, the examiner scored the used strategy for drawing. The obtained test scores were compared to the available normative data and calculated into z-scores. The neuropsychological testing took about 80 minutes.

Results

A total of 29 male, HIV-infected patients was included in this study. The participants were all able to complete the full neuropsychological test battery. Two participants refused to execute the PASAT. One participant had the Slovakian nationality. Test instructions were well-understood, however, tests which relied too much on language (COWAT and Categorical fluency) were excluded from the analyses.

Table 2 summarizes the demographic and clinical characteristics of the sample. Mean age was 41.7 (SD=6.7). Average amount of years of education was 16.9 (SD=.8). The median of CD4 nadir in this sample was 282. The lowest level of CD4 nadir was 43, the highest was 927. The viral load, the amount of virus-cells detectable in the blood, was undetectable for all participants, indicating they are stable on cART. The median for time of infection in months is 87. The minimum was 12 months, the maximum was 355 months. All participants succeeded a professional education and were pursuing a professional career.

Table 2. Demographic and clinical characteristics.

Demographic variable	M (SD)	Mdn	Range
Age	41.7 (6.7)		[27-50]
Education	16.6 (.8)		[15-18]
CD4 nadir		282	[43-927]
Time (months)		87	[12-355]

First, the cognitive profile of this sample was analyzed. In total, there were 11 out of 29 people with at least one test score 2SD's below the mean. As shown in Figure 1, there was 1 participant with only one deficit in the domain Speed; 1 participant with one deficit in the Executive functioning; 2 participants with deficits in the Attention/Working memory domain; 4 participants with deficits in the domain Speed and the domain Attention/Working memory; 1 participant with deficits in the domain Speed and the domain Learning/Memory; 1 participant with deficits in the domain Speed, Executive functioning and Learning/Memory; 1 participant with deficits in Speed, Attention/Working memory and Learning/Memory. Most overlap was found between the Speed and Attention/Working memory domains.

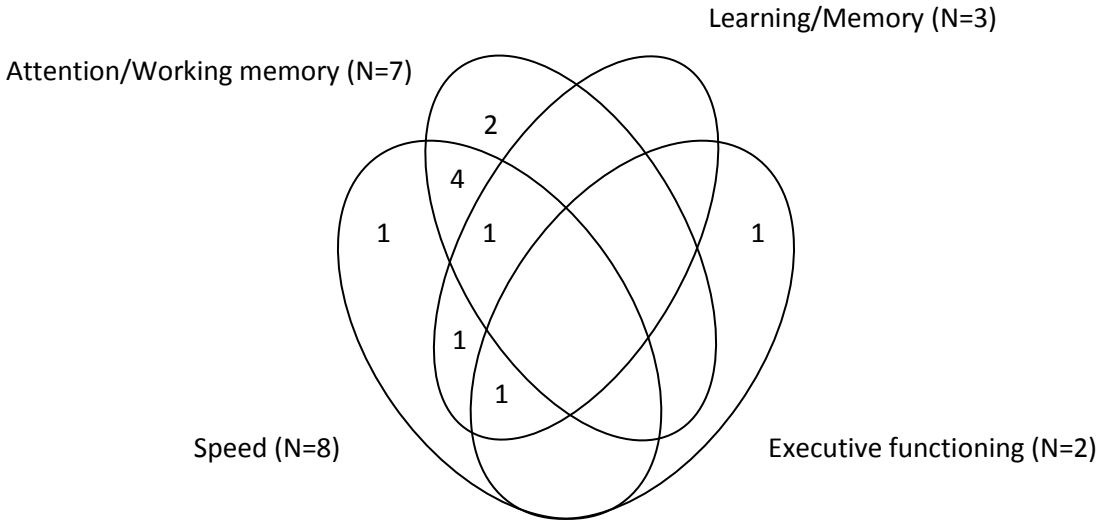

Figure 1. Venn diagram of distinct and overlapping deficits in the cognitive ability areas.

The cognitive profile was further analyzed, as shown in Table 3. The average global z-score of this sample was 0 (SD=0.6). The median of the Executive functioning domain was 0.2, with a minimum of -1.4 and a maximum of 1.3. The Attention/Working memory was on average -0.2 (SD=0.7). The median of the Learning/Memory domain was 0.2, with a minimum of -3 and a maximum of 1.7. The mean of the Speed domain was -0.1 (SD=1). Participants were divided into an impaired or unimpaired group, depending on their performance; in case of a single test-score 2SD's below the mean, they were signed to the impaired group, otherwise they were signed to the unimpaired group. The domain Speed was most impaired in the impaired group (M=-1.1, SD=0.8), followed by the Attention/Working memory domain (M=-0.7, SD=0.8). Executive functioning was on average -0.2 (SD=0.5), and the median of the Learning/Memory Domain was -0.1, with a minimum of -3, and a maximum of 0.7.

Table 3. Means and standard deviations in z-scores of each of the tests, domains and impaired/unimpaired group.

	All (N=29)	**Impaired (n=11)**	**Unimpaired (n=18)**
	M (SD)	**M (SD)**	**M (SD)**
Total Z-score	0 (0.6)	-0.6 (0.5)	0.4 (0.2)
Executive functioning	0.2 (0.5)	-0.2 (0.5)	0.43 (0.3)
Controlled Oral Word Association Test	0.2 (1.3)	-0.4 (1)	0.8 (1.3)
Category fluency – Animals	0.3 (0.9)	0.1 (0.6)	0.4 (0.9)
Brixton Spatial Anticipation Test	0.3 (1.5)	-0.6 (1.9)	1 (0.9)
Strategy Rey Complex Figure	0 (0)	0 (0)	0 (0)
Rey Complex Figure Test copy	0 (0.48)	-0.1 (0.6)	0 (0.4)
Attention /Working memory	-0.2 (0.7)	-0.7 (0.8)	0.1 (0.5)
Trailmaking Test Part B	0 (0.9)	-0.1 (1)	0 (0.9)
Visual Elevator Accuracy	0.2 (1)	0 (1.1)	0.5 (0.9)
Paced Auditory Serial Addition Test	-0.9 (1.3)	-1.9 (1.4)	-0.1 (0.8)
WAIS-IV NL LNS	0 (1.1)	-0.8 (1.1)	0.6 (0.8)
Learning/Memory	0.1 (0.8)	-0.3 (1.1)	0.3 (0.6)
Rey Auditory Verbal Learning Test	0.6 (1)	0.2 (1.1)	0.7 (0.8)
Rey Auditory Verbal Learning Test recall	0.2 (0.9)	0.2 (1.1)	0.1 (0.8)
Rey Complex Figure Test recall	-0.6 (1.1)	-1.2 (1.3)	-0.3 (0.7)
Speed of information processing & Motor Speed	-0.1 (1)	-1.1 (0.8)	0.5 (0.6)
Visual Elevator Speed	0.1 (1.5)	-0.5 (1.5)	0.4 (1)
Digit Symbol WAIS-IV NL	-0.2 (1)	-1.1 (0.7)	0.4 (0.6)
Symbol Search WAIS-IV NL	-0.2 (1.2)	-1.2 (0.9)	0.5 (1)
Trailmaking Test Part A	0.2 (1.8)	-1.2 (3.7)	1.3 (0.9)
Grooved Pegboard Time (dominant)	0 (-1.2)	-1 (1.3)	0.6 (0.8)
Grooved Pegboard Time (non-dominant)	-0.4 (-1.7)	-1.5 (2)	0.4 (1.1)

Clinical and demographic differences between the impaired and unimpaired group were analyzed, as shown in Table 4. A t-test was used to test for differences in age between the unimpaired (M=40.5, SD=6.9) and the impaired group (M=43.2, SD=5.3). There was no significant difference in age between the groups *t* (29)= .26, *ns*, *r*= .12. As years of education, CD4 nadir and duration of illness were not normally distributed, a Mann Whitney U was used to test for differences between the impaired and unimpaired group. There was no significant difference in years of education between the unimpaired (*mdn*= 17) and the impaired group (*mdn*=16), *U*=63, *z*= -1.99, *ns*, *r*=-.37. There was no significant difference between levels of CD4 nadir in the unimpaired group (*mdn*=301) and the impaired group (M=248.2), *U*= 73, *z*=-1.2, *ns*, *r*=-.22. There was no significant difference between duration of illness in the unimpaired group (*M*=70.5) and the impaired group (*mdn*=101), *U*= 72,*z*=-1.2, *ns*, *r*=-.22.

Table 4. The *z* and *p*-values of clinical and demographic characterstic differences between the unimpaired and impaired group.

	Unimpaired (n=18) m (sd)	**Impaired (n=11)** m (sd)	***z*-value/*p*-value**	**Effect size** (Pearson's *r*)
Age	40.5 (6.9)	43.2 (5.3)	0.6	0.12
Years of education	Mdn= 17 Range= 16-18	Mdn= 16 Range= 15-18	0.07	-0.37
CD4 Nadir	Mdn= 301 Range= 43-927	Mdn= 242 Range= 147-363	0.2	-0.22
Duration of illness in months	Mdn = 75 Range =12-155	Mdn= 101 Range= 37-355	0.2	-0.22

Discussion

As the participants in this sample succeeded a professional education, have mentally demanding jobs, and are fully participating in society, this sample might represent a high-functioning subgroup of the HIV-infected population. As there has not been a study conducted on this subgroup yet, our first aim was to explore cognition in highly educated, HIV-infected, virologically suppressed males. Results showed the domain Speed was most impaired in this sample. This can be explained by a study from Pfefferbaum et al. (2014), who showed that the aging HIV-infected brain has frontal-striatal damage similar to much older 'normal' aging subjects. As 'normal' aging usually starts with a decline in speed of information processing (Salthouse, 2010), and the HIV-infected brain is damaged similar to a much older 'healthy' brain, one could argue the domain Speed will be most impaired. This is in line with our results. However, the aging brain and its clinical presentation is also related to the amount of cognitive reserve an individual has. Cognitive reserve can be defined by the amount of brain damage an individual can handle before clinical presentation of this damage is noticed in daily life (Stern, 2002). It is also possible that this high-functioning subgroup of the HIV-infected population is showing a different cognitive profile compared to other studies, because of a different amount of cognitive reserve. For example, Heaton et al. (2015) showed in a follow-up study that IQ is a protective factor of cognitive abilities regarding cognitive decline in HIV-infected individuals. A similar pattern was shown by Hall et al. (2007), where higher levels of education delayed the onset of cognitive decline in healthy individuals. Furthermore, Bosma et al. (2003), showed that people with mentally demanding jobs had lower risks of developing cognitive impairment. As all participants in this sample succeeded a professional education and pursued a professional career, these could be protective factors of the (HIV-related) cognitive decline in this sample, therefore generating a different cognitive profile. Whether the cognitive profile of this high-functioning subgroup of HIV-infected males is due to HIV-associated acceleration of aging of the brain or the amount of cognitive reserve the participants in this sample have, remains unclear. It is therefore incredibly important to keep studying this sample to see whether this high-functioning subgroup continues to show a distinct cognitive pattern.

Even though the participants claimed not to experience cognitive impairment, results showed a substantial amount of cognitive deficits in this sample. There were no indications for lack of motivation or lack of disease-insights in this sample. A possible explanation could be that the damage to the frontal-striatal pathway has an insidious onset, meaning it could take a while before it is noticed by the participants. Participants could therefore have anticipated on this and have learned themselves to cope with the slower speed of information processing, hence not noticing impairment (yet).

The second aim of this study was to examine whether duration of illness and CD4 nadir affect cognition. As HIV is now well-treated by cART, people with HIV now become older, facing an aging process burdened by the HIV-infection. We therefore expected the participants with cognitive impairment to have a longer duration of illness compared to the participants without cognitive impairment. Also, as CD4 nadir has shown to be a predictor of worse cognitive impairment (Ellis et al., 2011), we expected the participants with impaired cognition to have lower levels of CD4 nadir than the unimpaired group. However, none of these hypotheses were confirmed. Regarding CD4 nadir levels, it was shown by Van Sighem & Op de Coul (2014) that most patients in The Netherlands had much higher levels of CD4 nadir compared to our sample. Therefore, we think we could not find any differences in CD4 nadir levels because of a floor-effect. Regarding duration of illness, it appears not to affect cognition in this sample. As all participants succeeded a professional education of nearly the same amount of years, we could not find a difference in levels of education. Even though there seems to be a trend, due to the very small differences in years of education, this should not be seen as one.

Limitations & Future research

This study was part of a medication-switch study, where 2/3 of the participants were asked to switch medication to a non-efavirenz containing medicine. This might have induced a participation bias, resulting in mostly high educated patients. On the other hand, this sample is fairly representative of the HIV-infected population in The Netherlands (Van Sighem & Op de Coul, 2014). For a better understanding of cognition in HIV-infected males in the Dutch population, we do suggest to include a larger group of patients.

As mentioned before, we suggest to do a follow-up study in the next 5-10 years. Especially because it has been shown that once cognitive decline begins, it is more rapid in people with higher education (Hall et al., 2007). Regarding this, it might also be interesting to expand the age band, hence including older patients.

Conclusion

When cognitive impairment was present, the domain Speed was most affected in this sample of high-functioning HIV-infected, virologically suppressed males. It remains unclear whether the present cognitive profile is due to HIV-associated acceleration of aging of the brain, or the influence of the relatively large amount of cognitive reserve of the participants. Further research is needed to study for the continuation of this distinct cognitive profile in this high-functioning subgroup of the HIV-infected population.

References

An, S.F., Groves, M., Gray, F., Scaravilli, F. (1999). Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals. *Journal of neuropathology and experimental neurology, 58, 1156–1162.*

Bosma, H., Van Boxtel, M.P.J., Ponds, R.W.H.M., Houx, P.J., Burdorf, A. & Jolles, J. (2003). Mental work demands protect against cognitive impairment: MAAS prospective cohort study. *Experimental Aging Research, 29(1), 33-45.*

Burgess, P.W. & Shallice, T. (1997). *The Hayling and Brixton tests* [measurement instrument]. England: Thames valley test company.

Carey, C., Woods, S., Rippeth, J., Gonzalez, R., Moore, D., Marcotte, T., Grant, I.& Heaton, R.K. (2004). Initial validation of a screening battery for the detection of HIV-associated cognitive impairment. *The clinical neuropsychologist, 18 (2), 234-248.*

Cohen, R.A., Seider, T.R. & Navia, B. (2015). HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimer's research & therapy 7 (37), 1-10.*

Cooper, A., García, M., Petrovas, C., Yamamoto, T., Koup, R. & Nabel, G.(2013). HIV-1 causes CD4 cell death through DNA-dependent protein kinase during viral integration. *Nature, 498, 376-379.*

Diamond, A. (2013). Executive functions. *Annual review psychology, 64, 135-168.*

Dore, G.J., McDonald, A., Li, Y., Kaldor, J.M. & Brew, B.J. (2003). Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS, 17 (10), 1539-1545.*

Durvasula, R.S., Miller, E.N., Myers, H.F.,& Wyatt, G.E. (2001). Predictors of neuropsychological performance in HIV positive women. *Journal of clinical and experimental neuropsychology, 23, 149-163.*

Ellis, R.J., Badiee, J., Vaida, F., Letendre, S., Heaton, R.K., Clifford, D., Collier, A.C., Gelman, B., McArthur, J., Morgello, S., McCutchan, J.A. & Grant, I. (2011). CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS, 25 (14), 1747-1751.*

Elst van der, W., Van Boxtel, M.P.J., Van Breukelen, G.J.P. & Jolles, J. (2006). Normative data for the animal, profession and letter m naming fluency tests for Dutch speaking participants and the effects of age, education, and sex. *Journal of the international neuropsychological society, 12, 80-89.*

Grant, I. (2008). Neurocognitive disturbances in HIV.*International review of psychiatry, 20, 33-47.*

Gronwall, D. & Sampson, H. (1974). *The psychological effects of concussion* [measurement instrument]. Auckland: Auckland University.

Hall, C.B., Derby, C., LeValley, A., Katz,M.J., Verghese, J. & Lipton, R.B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology, 60, 1657-1664.*

Heaton, R.K., Clifford, D.B., Franklin, D.R. Jr., Woods, S.P., Ake, C., Vaida, F., et al. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology, 75, 2087–2095.*

Heaton, R.K., Franklin Jr, D.R.F., Deutsch, R., Letendre, S., Ellis, R.J., Casaletto, K., Marquine, M.J., Woods, S.P., Vaida, F., Atkinson, J.H., Marcotte, T.D., McCutchan, J.A., Collier, A.C., Marra, C.M., Clifford, D.B., Gelman, B.B., Sacktor, N., Morgello, S., Simpson, D.M., Abramson, I., Gamst, A.C., Fennema-Notestine, C., Smith, D.M. & Grant, I. (2015). Neurocognitive Change in the Era of HIV Combination Antiretroviral Therapy: The Longitudinal CHARTER Study. *HIV/AIDS, 60, 473-480.*

Kumar, A.M., Borodowsky, I., Fernandez, B., Gonzalez, L., Kumar, M. (2007). Human immunodeficiency virus type 1 RNA Levels in different regions of human brain: quantification using real-time reverse transcriptase-polymerase chain reaction. *Journal of Neurovirology, 13, 210–224.*

Maartens, G., Celum, C. & Lewin, S.H. (2014). HIV infection: epidemiology, pathogenesis, treatment, and prevention. *Lancet, 384, 258-271.*

Noordt van der, M.& Op de Coul, E.L.M.(2014). Aids en hiv-infectie: Zijn er verschillen tussen Nederland en andere landen? *Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid*. Bilthoven: RIVM.

Pfefferbaum, A., Rogosa, D.A., Rosenbloom, M.J., Chu, W., Sassoon, S.A., Kemper, C.A., Deresinski, S., Rohlfling, T., Zahr, N.M. & Sullivan, E.V. (2014). Accelerated aging of selective brain structures in human immunodeficiency virus infection: a controlled, longitudinal magnetic resonance imaging study. *Neurobiology of aging, 35 (7), 1755-1768.*

Plessis du, S., Vink, M., Joska, J.A., Koutsilieri, E., Stein, D.J., Emsley, R. (2014).HIV infection and the fronto-striatal system: a systematic review and meta-analysis of fMRI studies. *AIDS, 28, 803-811.*

Rey, A. (1941). The Rey Auditory Verbal Learning Test. L'examen psychologique dans les cas d'encéphalopathie traumatique. *Archives de Psychologie, 28, 286-340.*

Reitan, R. M., & Wolfson, D. (1985). *The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation* [measurement instrument]. Tucson: Neuropsychological Press.

Robertson, I.H., Ward, T., Ridgeway, V. & Nimmo-Smith, I. (1994). *The test of everyday attention* [measurement instrument]. England: Thames valley test company.

Roy, E. A., & Square-Storer, P. A. (1994). *Neuropsychology of movement sequencing disorders and apraxia* [measurement instrument]. St. Louis: Academic Press.

Salthouse, T.A. (2010). Selective review of cognitive aging. *Journal of international neuropsychological society, 16(5): 754–760.*

Schmand, B., Groenink, S.C. & Van den Dungen, M. (2008). Letterfluency: psychometrische eigenschappen en Nederlandse normen. *Tijdschrift voor gerontologie en geriatrie, 39, 64-76.*

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the international neuropsychological society, 8, 448-460.*

Van Sighem, A. & Op de Coul, E. The HIV epidemic in the Netherlands [in Dutch]. In: Van Sighem, A., Gras, L., Smit, C., Stolte, I. & Reiss, P., editors. *Monitoring report 2014: human immunodeficiency virus (HIV) infection in the Netherlands.* Amsterdam: Stichting HIV Monitoring, Academic Medical Centre.

Singh, N., et al. (2013). HIV encephalopathy and AIDS dementia complex. *Medscape, drugs & diseases.* Retrieved from http://emedicine.medscape.com/article/1166894-overview.

Wechsler, D. (2013). *Wechsler adult intelligence scale – fourth edition – nederlandstalige bewerking* [measurement instrument]. Amsterdam: Pearson inc.