Neuropsychological deficits in adult HIV infected postnatally: a pilot study in patients with hemophilia

Silvia Riva (silvia.riva1@unimi.it)
Department of Health Science, University of Milan, via A. di Rudinì 8 Milan, Italy

Ilaria Cutica (ilaria.cutica@unimi.it)
Department of Health Science, University of Milan, via A. di Rudinì 8 Milan, Italy

Gabriella Pravettoni (gabriella.pravettoni@unimi.it)
Department of Health Science, University of Milan, via A. di Rudinì 8 Milan, Italy
European Institute of Oncology (IEO), Milan, Italy

Abstract

Despite advances in the management of HIV infection with the introduction of combination antiretroviral therapy (cART), it is well known that HIV can directly infect the central nervous system (CNS) and, as a result neuropsychological impairments can be manifested.
However, in literature there are contrasting results on which cognitive functions are mainly affected, especially when different HIV seropositive populations are considered. In this study, we seek to determine whether seropositivity is associated with a poor neuropsychological performance in patients infected postnatally, namely haemophilic patients. The results suggest that HIV infection is associated with deficits in attention, short term spatial memory, phonemic fluency, abstraction and visual recognition. Such results have important implications for day-to-day functioning, as the level of impairment detected may cause difficulties in completing common everyday tasks.

Keywords: HIV seropositivity; neuropsychological impairments; haemophilia.

Introduction

Although neuropsychological profiles vary amongst HIV+ individuals, several estimates indicate that as many as 50% of HIV+ individuals display some degree of neuropsychological impairment when impairment is derived from comparisons with normative performance standards (e.g., Dawes, Suarez, Casey, Cherner et al., 2008). A recent meta-analysis revealed that the most severe forms of HIV associated neuropsychological impairments have decreased since the widespread use of combination antiretroviral therapy (cART): Al-Khindi and colleagues (2011) found less attentional, motor, and executive skill impairments in HIV+ individuals treated with cART. Notwithstanding, several studies revealed that impairments in learning (e.g., Carey, Woods, Rippeth, Heaton et al., 2006; Maki, Cohen, Weber, Little et al., 2009), verbal memory (Seider, Assawin Gongvatana, Devlin et al., 2014) and prospective memory (e.g., Doyle, Loft, Morgan, Weber et al., 2013; Martin, Nixon, Pitrak, Weddington et al., 2007) still occur even in patients treated with cART (e.g., Grant et al., 2014; Heaton, Clifford, Franklin, Woods et al., 2010). Also, the longitudinal observation of these patients has given contrasting results: some studies have not shown any decline in neurocognitive functions (Grassi Clerici, Perin, Zocchetti et al., 1995; Selnes, Miller, McArthur, Gordon, et al., 1990) while others have (Applebaum, Otto, Richardson, & Safren, 2010; Ayuso-Mateos, Pereda, Del Barrio, Echevarria et al., 2000; Woods Iudicello, Moran, Carey et al., 2008;).

In addition, some authors have argued that such difficulties might be more related to the presence of important covariates, such as CD4 nadir count (Ellis, Badiee, Vaida, Letendre et al., 2011; Heaton, Franklin, Ellis, McCutchan et al, 2011), the time of infection (Ettenhofer, Hinkin, Castellon, Durvasula et al., 2009), drug abuse (Shimizu, Chow, Valcour, Masaki et al., 2011), cranial traumas, and several psychological alterations, rather than to the direct action of HIV virus.

In our view, it is important to notice that neuropsychological impairments have been mainly studied in two HIV seropositive (henceforth, HIV+) populations:

- patients infected vertically or perinatally (e.g. through breast milk), a condition that presents adjunctive cognitive disorders linked to neuro-developmental growth changes (Rondanelli, Caselli, Arico, Maccabruni et al., 2002; Van Rossum, Gaakeer, Verweel, Hartwig et al., 2003) and neurological changes (Antinori, Arendt, Becker, Cherner et al, 2007);
- patients who contracted the infection postnatally or in adulthood, often comprises participants who presented other types of confounding factors, such as cocaine and opiates use, alcohol abuse (Buttner, 2011; Byrd, Robinson-Papp, Rivera Mindt, Mintz et al., 2013;Lundqvist, 2010), and different risk behaviours (De Ronchi, Faranca, Berardi, Scudellari et al., 2002).

By contrast, a population of HIV patients generally infected postnatally at an older age, and that usually do not present the drug-user populations confounding factors, consists of patients medically induced to HIV infection through blood transfusions (Ettenhofer, Hinkin, Castellon, Durvasula, et al., 2009). Hemophiliacs treated with factor

infusions before 1985 have been at risk of acquiring HIV (Brookmeyer & Goedert, 1989): several studies have shown that about 60–80% of patients with hemophilia, exposed to infected blood concentrates, contracted the HIV virus (e.g., Goedert, 1995).

The interest in neurocognitive dysfunctions in hemophilia HIV+ patients is quite innovative in the literature. Findings are often inconsistent and difficult to summarize (for a review, see Riva, Cutica, Pravettoni, 2014); most of the early research findings are based on the Hemophilia Growth and Development Study (HGDS; Hilgartner, Donfield, Willoughby, Contant et al., 1993), a multicenter study of the long-term effects of HIV infection on growth and neurodevelopment in HIV+ hemophilia children and adolescent, that found that such patients did not differ significantly from HIV- hemophilic controls on a variety of neuropsychological tests. However, as indicated in follow-up studies of HGDS patients (Iudicello, Woods, Weber, Dawson et al., 2008; Loveland, Stehbens, Mahoney, Sirois et al., 2000; Watkins Cool, Usner, Stehbens, et al. 2000) there was a significant decline in neurocognitive functions such as memory, attention and language over 5 years, directly related to a decline in immune functioning and to socio-educational covariates such as school absenteeism and a poorer academic achievement that frequently marked these young patients.

Although there are some data available in the context of paediatric populations, studies are totally underrepresented in the adult population with mixed and confusing results (e.g., Riedel, Helmstaedter, Bülau, Durwen et al., 1992). Some studies found cognitive impairment in attention, motor skills, and visual performance in HIV+ haemophiliacs to be related to the decrement of immunological functioning, especially when the CD4+ cell count was lower than 200/mm3 (e.g., Blanchette, Smith, King, Fernandes-Penney et al., 2002). No clear data on cognitive impairment of HIV+ haemophiliacs with CD4+ cell count higher than 200 are available.

The present study aimed to assess the presence and the extent of neuropsychological impairments in such a patients' group.

Method

Participants

Fifteen HIV+ male haemophiliacs (mean age 45±8.4) were administered neuropsychological tests. Patients were recruited through their treating physicians via the haemophilia and thrombosis outpatient clinics in three Italian centres. The inclusion criteria were as follow: diagnosis of haemophilia, diagnosis of HIV with CD4+ counts consistently > 200cells/mm3, treatment with cART, age > 18. Exclusion criteria were diagnosis of AIDS, serious mental illness with a certificated diagnosis (e.g., major depression, anxiety, bipolar disorder) or known central nervous system pathology, including progressive multifocal leukoencephalopathy, brain cancer, neurosyphilis, active cytomegalovirus infection, multiple sclerosis, stroke, seizures/epilepsy, drug use.

Tests were also administered to a control group consisting of fifteen adults (mean age 49,3±6.84), comparable for age and education (Mann–Whitney test: z=-1.41, p=.16; z=-.35, p=.77, respectively). Participants' educational and professional characteristics are presented in Table 1.

Table 1. Patients' and controls' educational and employment characteristics

		HIV+ haemophiliacs (n = 15)	Controls (n = 15)
Educational level	Primary school	1	-
	Secondary school	8	9
	High School	5	4
	University	1	2
Currently occupied		9	11

Material

Participants completed six neuropsychological tests from the Italian Brief Neuropsychological Examination battery (ENB: Mondini, Mapelli, Vestri, Arcara, et al., 2003) to investigate:

- visual attention and cognitive processing speed (Trail Making Test A, in which participants have to connect a series of 25 number in ascending order as quickly as possible: Tombaugh, 2004);
- visual attention and executive functioning (Trail Making Test B, in which participants have to alternate between numbers and letters (1, A, 2, B, etc.) connecting them in sequential order as quickly as possible:Tombaugh, 2004);
- digit span memory (Letter-Number Sequencing from the WAIS-III, which measures the number storage capacity of the working memory: Weschler, 1995);
- phonemic fluency (Verbal Fluency test, in which participants have to say as many words beginning with a certain letter as possible in 60 seconds: Lezak, 1995),
- abstraction (Italian Test of abstraction from the ENB, in which, given three words, the participant have to tell what the three concepts have in common: Mondini, et al., 2003).
- visual recognition (Rey Tangled Lines Task, in which participants have to recognize the greatest possible number of figures within a table in which the figures are drawn tangled: Rey, 1964).

Procedure

Patients were met immediately after a routine medical appointment, in which –among other things- overall clinical status, including the presence of concomitant diseases, was evaluated. After signing the data protection form, they were presented with the neuropsychological tests; each of them

dealt with the tests individually in a quiet room. According to each test requirements, the answers were recorded either by the patient or by the experimenter. Patients completed the tests in about twenty minutes. Controls were tested individually in a quiet room; they completed the test in about twenty minutes.

Results

As only three test out of six have the corrected score that allows to correct raw scores for age and educational level, we decided to analyse the raw data for all the tests, also considered that age and education do not differs in the two groups.

Between groups comparisons. Table 2 shows the mean raw data for each neuropsychological test, for patients and controls.

Table 2. Mean raw scores patients and controls (standard deviation in parentheses)

Tests	Patients (n =15)	Controls (n=15)
Trial Making Test A	60.93seconds* (24.52)	32.27 seconds (8.54)
Trial Making Test B	173.53seconds (63.39)	92.73 seconds (9.59)
Digit Span memory	3.93 items (1.71)	5.87 items (.74)
Phonemic fluency	27.53 words (6.20)	34.14 words (5.06)
Test of abstraction	4.40 abstr. (1.29)	5.73 abstr. (.46)
Rey Tangled Lines Task	25.19 figures (1.20)	4.67 figures (.62)

* In Trial Making Test A and B, a longer time corresponds to a worst performance

Results show that patients' performance in each neuropsychological test is worse than the corresponding performance by healthy controls. More in detail, we found that patients performed significant worse than controls in Trail Making A (T-test: t= 3.53, p=.001), in Trail Making B (T-test: t= 4.88, p<.0001), in Digit Span (T-test: t=-4.02, p<.0001), in Phonemic Fluency (T-test: t= -3.19, p=.003), and in Rey Tangled Test (T-test: t=-5..836, p<.0001).

Within-group comparisons. As the HIV literature reveals a correlation between cognitive disorders and patients' socio-demographic factors such as education and job status, we performed some comparisons to figure out whether the same effect holds for our participants. We thus divided both groups into two into sub-groups according to the educational level. We considered participants with 5 to 8 education years as "low educational level", and participants with 13 to 18 years as "high educational level". Nine patients and 9 controls fell into the low educational level, and 6 patients and 6 controls into the high educational level. Low school level patients performed worse than the high education group only in Trial Making B Test (Mann-Whitney Test: z=-2.125, p=.036).

We then divided patients according to their occupational status: employed individuals on one side (n=9) versus unemployed or with disability pension individuals (n=6). We found that the unemployed/disability pension group has a worse performance than the employed group only in Trial Making A Test (Mann-Whitney Test: z=-2.239; p=.026).

As these results were inconsistent with most of the existing literature, in addition we performed an ANCOVA analysis, controlling for the effect of age, education and working status. The analysis controlled for such covariates revealed that patients performed worse than controls on Attention with regard to the Trail Making A Test (F=8.470, p=.005), and Trail Making Test B (F=5.811, p=.022). However, the predicted main effect of education was not significant (F=4.89, p = .066, ηp2 = .004), neither was the predicted main effect of working status (F=.595, p = .455, ηp2= .004), and nor the main effect of age (F= 1.226, p = .292, ηp2 = .004). Although the introduction of covariates reduced the distance between the two groups of participants, they did not eliminate the effect of HIV infection on neuropsychological impairment completely. Therefore the presence of these covariates (age, educational level and working status) did not explain group differences *per se*.

Discussion

Although neuropsychological impairments are well described in some specific HIV populations, very few studies investigated the cohort of adults seropositive patients with haemophilia, especially in the cART era. Furthermore, the few existing studies on children and adolescents, and on adults before the widespread use of cARTs, often obtain inconsistent results.

Our pilot study, conducted on a small but well-controlled sample of HIV + hemophiliacs, reveals that such patients show signals of neuropsychological impairments when compared with the controls' performances.

In particular, considering the whole group of HIV+ patients, we found an HIV detrimental effect on tests requiring attention and rapid information processing (Trail Making Test A, and Trail Making B for patients with low educational level), consistently with the classic conceptualization of HIV as a subcortical disease targeting frontal-striatal circuits supporting these abilities (e.g., Baldewicz, Leserman, Silva, Petitto et al., 2004; Reger, Welsh, Razani, Martin et al., 2002).

Patient's results on these two attention tasks, on the visual recognition task (Rey Tangled Lines), and on phonemic fluency are also consistent with one of the two existing study on adult seropositive hemophiliacs, by Riedel and colleagues (1992), who found that patients are impaired in

visual attention, visuoperceptual speed, and verbal memory and fluency. However, they also found that patients' impairment was a linear relationship with the decreasing of immune functioning, whereas we found deficits also in patients with high immune functioning (as all our patients are).

Our patients' impairment on Digit span memory is in line with Riedel's work, and with several previous findings showing that deficits in memory, and in particular in short term memory, are among the strongest cognitive complain in HIV (non-haemophilic) patients (e.g., Doyle Suarez, Casey, Cherner et al., 2013; Maki, Cohen, Weber, Little et al., 2009; Seider et al., 2014). Also, our data are consistent with results from the other existing study on adults seropositive haemophiliacs, a case-study of four patients (Turnbull, Saling, Kaplan-Solms, Cohn, et al, 1991), according to which patients are impaired in visual memory and spatial perception.

The HIV literature reveals a correlation between cognitive disorders and socio-demographic factors (job status and education); however, we did not find such interactions. Further studies will be needed to understand these results.

Taken together, our results reveal that also HIV+ hemophiliacs are impaired in several cognitive functions, as it happens to HIV+ patients infected vertically, as well as to patients infected in adulthood. This result suggests that the cognitive impairments might be related predominantly to the direct effect of the HIV virus, and that they are relatively independent from the age of infection and from confounding factors (such as drug abuse). However, the study is limited by its design as a pilot study, and it suffers from methodological challenges, such as potential instability of the data related to the small sample size. Future studies, with larger samples, should be conducted to replicate these findings and test for potential interaction effects among variables of interest.

Furthermore, future studies are needed to compare these results with those obtained by a group of seronegative hemophiliacs, to investigate to what extent the combination of both diseases could affect the results obtained.

Another limitation of this study is the lack of data on MRI abnormalities and other neurological indicators which made it impossible to link the neuropsychological assessment results with some neurobiological correlates or other medical observations.

On the other hand, the current study is strengthened by selective inclusion criteria (such as the level of CD4 > 200, and the absence of a psychiatric disorder such as a diagnosis of depression/anxiety), that allows the evaluation of a precise and representative cohort. It considerably enriches the currently scarce literature on European samples of HIV+ haemophiliac adult patients in the cART era.

The level of neuropsychological impairment we detected have relevant implications for day-to-day patients' functioning: for instance they may cause difficulties in completing common everyday tasks, such as maintaining adherence to complex medication regimens (both for haemophilia and HIV), as well as holding down a full-time job. Continued research into the mechanisms related to HIV seropositivity and neurocognitive dysfunction may provide targets for meaningful interventions.

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References

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

Antinori, A., Arendt, G., Becker, J.T., Cherner, M., Clifford, D.B., et al. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology, 69*: 1789–1799.

Ayuso-Mateos, J.L., Pereda, M., Del Barrio, A., Echevarria, S., Farinas, M.C., and Garcia Palomo, D. (2000). Slowed reaction time in HIV-1 seropositive intravenous drug users without AIDS. *European Neurology, 44*, 72-8.

Applebaum, A.J., Otto, M.W., Richardson, M.A., and Safren, S.A. (2010) Contributors to neuropsychological impairment in HIV-infected and HIV-uninfected opiate-dependent patients. *Journal of Clinical Experimental Neuropsychology, 32*, 579–589

Baldewicz, T.T., Leserman, J., Silva, SG, Petitto, J., Golden, R.N., Perkins, D.O., & Evans, D.L. (2004). Changes in neuropsycho-logical functioning with progression of HIV-1 infection: Results of an 8-year longitudinal investigation. *AIDS and Behavior, 8*: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*:223-241.

Brookmeyer, R., & Goedert, J.J. (1989). Censoringinan epidemic with an application to hemophilia-associated AIDS. *Biometrics* 45, 325–335.doi:10.2307/ 2532057

Buttner, A. (2011). Review: The neuropathology of drug abuse. *Neuropathology and Applied Neurobiology, 37*:118–134.

Byrd, D.A., Robinson-Papp J., Rivera Mindt, R., Mintz, L., Elliott, K., Lighty, Q., & Morgello S. (2013). Isolating Cognitive and Neurologic HIV Effects in Substance-Dependent, Confounded Cohorts: A Pilot Study. *Journal of the International Neuropsychology Society, 19*: 463-673.

Carey, C.L., Woods, S.L., Rippeth, J.D., Heaton, R.K., Grant I, & The Hiv Neurobehavioral Research Center (HNRC) Group. (2006). Prospective memory in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology, 28*: 536–548.

Dawes, S., Suarez, P., Casey, C.Y., Cherner, M., Marcotte, T.D., Letendre, S., Grant, I., et al. (2008). Variable patterns of neuropsychological performance in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology, 30*: 613–626.

De Ronchi, D., Faranca, I., Berardi, D., Scudellari, P., Borderi, M., Manfredi, R., & Fratiglioni, L., (2002). Risk Factors for cognitive impairment in HIV-1-Infected persons with different risk behaviours. *Archives of Neurology, 59*: 812-818.

Doyle, K.L., Loft, S., Morgan, E.E., Weber, E., Cushman, C., Johnston, E., Grant, I., et al., (2013). Prospective memory in HIV-associated neurocognitive disorders (HAND): The neuropsychological dynamics of time monitoring. *Journal of Clinical and Experimental Neuropsychology, 35*: 359-372.

Ellis, R.J., Badiee, J., Vaida, F., Letendre, S., Heaton, R.K., Clifford, D., Collier, C.A., et al. (2011). CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS 25*: 1747–1751.

Ettenhofer, M.L., Hinkin, C.H., Castellon, S.A., Durvasula, R., Ullman, J., Lam, M., Myerset, H., et al. (2009). Aging, neurocognition, and medication adherence in HIV infection. *American Journal of Geriatric Psychiatry, 17:* 281–290.

Giesbrecht, C.J., Thornton, A.E., Hall-Patch, C., Maan, E.J, Cote, H.C.F., Money, D.M., & Pick, X.N.(2014). Select Neurocognitive Impairment in HIV-Infected Women: Associations with HIV Viral Load, Hepatitis C Virus, and Depression, but Not Leukocyte Telomere Length. *PLoS ONE 9(3):* e89556.

Grant, I., Franklin, D. R., Deutsch, R., Woods, S. P., Vaida, F., Ellis, R. J., ... & Heaton, R. K. (2014). Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology*, *82*(23), 2055-2062.

Grassi, M.P., Clerici, F., Perin, C., Zocchetti, C., Borella, M., Cargnel, A., Mangoni, A. (1995). HIV infection and drug use: influence on cognitive function. *AIDS. 9*, 165-170.

Goedert, J. (1995). Mortality in haemophilia. *Lancet* 346, 1425–1426.doi:10.1016/ S0140-6736(95)92440-X

Heaton, R. K., Grant, I., Butters, N., White, D. A., Kirson, D., Atkinson, J. H., McCutchan, J.A., et al. (1995). The HNRC 500: Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society, 1:* 231–251.

Heaton, R.K., Clifford, D.B., Franklin, D.R. Jr, Woods, S.P., Ake, C., Vaida, F., Ellis, R.J., et al. (2010). HIV associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology, 75*: 2087–2096.

Heaton, R.K., Franklin, D.R., Ellis, R.J., McCutchan, J.A., Letendre, S.L., LeBlanc, S., Corkran, S.H., et al. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. *Journal of NeuroVirology, 17:* 3–16.

Heaton, R.K., Marcotte, T,D,, Mindt, M.R., Sadek, J., Moore, D.J., Bentley, H., McCutchan, J.A., et al. (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. *Journal of the International Neuropsychology Society, 10*:317-331.

Hilgartner, M. W., Donfield, S. M., Willoughby, A., Contant, C., Evatt, B., Gomperts, E., Hoots, K., et al. (1993). Haemophilia Growth and Development Study : Design, methods, and entry data. *American journal of Pediatric Hematology/Oncology, 15*: 208-218.

Iudicello JE, Woods SP, Weber E, Dawson MS, Scott JC, & The HIV Neurobehavioral Research Center (HNRC) Group (2008). Cognitive mechanisms of switching in HIV-associated category fluency deficits. *Journal of Clinical and Experimental Neuropsychology 30*: 797–804.

Lezak, M.D. (1995). *Neuropsychological assessment*. Oxford University Press, Oxford

Loveland, K. A., Stehbens, J. A., Mahoney, E. M., Sirois, P. A., Nichols, S., Bordeaux, J. D., Watkins, J. M., et al. (2000). Declining immune function in children and adolescents with Haemophilia and HIV infection: Effects on neuropsychological performance. *Journal of Pediatric Psychology, 25*: 309-322.

Lundqvist, T. (2010). Imaging cognitive deficits in drug abuse. *Current Topics in Behavioral Neurosciences, 3*:247–275.

Maki, P.M., Cohen, M.H., Weber, K., Little, D.M., Fornelli, D., Rubin, L.H., Perschler, P., et al. (2009) Impairments in memory and hippocampal function in HIV-positive vs HIV negative women. *Neurology 72*: 1661–1668.

Martin, E.M., Nixon, H., Pitrak, D.L., Weddington, W., Rains, N.A., Nunnally G.,Grbes S., et al. (2007) Characteristics of prospective memory deficits in HIV-seropositive substancedependent individuals: Preliminary observation, *Journal of Clinical and Experimental Neuropsychology 29*: 496–504.

Mondini S., Mapelli D., Vestri A., Arcara G., & Bisiacchi P.S. (2003). *Esame Neuropsicologico Breve*. Cortina Raffaello, Torino, Italy

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

Rey, A. (1964) *L'Examen clinique en psycologie.* (The clinical exam in psychology.) Presses Universitaires de France, Paris

Riedel, R.R., Helmstaedter, C., Bülau, P., Durwen, H.F., Brackmann, H., Fimmers, R., Clarenbach, P., et al.

(1992). Early signs of cognitive deficits among human immunodeficiency virus-positive haemophiliacs. *Acta Psychiatrica Scandinavica, 85*: 321–326.

Riva, S., Cutica, I., & Pravettoni, G. (2014). Is there evidence for neurocognitive dysfunctions in patients with postnatal HIV infection? A review on the cohort of hemophilia patients. *Frontiers in human neuroscience*, *8*.

Rondanelli M, Caselli D, Arico M, Maccabruni, A., Magnani, B., Bacchella, L., De Stefano, A., et al. (2002). Insulin-like growth factor I (IGF-I) and IGF-binding protein 3 response to growth hormone is impaired in HIV-infected children. *AIDS Research and Human Retroviruses*, *18*:331–339.

Seider T.R., Assawin Gongvatana X.L., Devlin, K.N., de la Monte S.,M., Chasman, J.D., Yan, P., Tashima, K.T., et al. (2014). Verbal memory declines more rapidly with age in HIV infected versus uninfected adults. *Journal of Clinical and Experimental Neuropsychology*, *36*:4, 356-367

Selnes, O. A., Miller, E., McArthur, J., Gordon, B., Munoz, A., Sheridan, K., ... & Saah, A. J. (1990). HIV-1 infection No evidence of cognitive decline during the asymptomatic stages. *Neurology*, *40*(2), 204-204.

Shimizu, S.M., Chow, D.C., Valcour, V., Masaki, K., Nakamoto, B., Kallianpur, K.J., & Shikuma, C. (2011) The impact of depressive symptoms on neuropsychological performance tests in HIV-infected individuals: A study of the Hawaii aging with HIV cohort. *World Journal of AIDS*, *1*:139–145.

Tombaugh Nichols, S., Mahoney, E.M., Sirois, P.A., Bordeaux, J.D., Stehbens, J.A., Loveland, K.A., Amodei, N., et al., (2000). HIV-Associated Changes in Adaptive, Emotional, and Behavioral Functioning in Children and Adolescents With Haemophilia: Results From the Haemophilia Growth and Development Study. *Journal of Paediatric Psychology, 25*, 545-556.

Turnbull, O., Saling, M. M., Kaplan-Solms, K., Cohn, R., & Schoub, B. (1991). Neuropsychological deficit in haemophiliacs with human immunodeficiency virus. *Journal of Neurology, Neurosurgery & Psychiatry*, *54*(2), 175-177.

Van Rossum, A.M., Gaakeer, M.I., Verweel, S., Hartwig, N.G., Wolfs, T.F., Geelen, S.P., Lamberts, S.W., et al. (2003). Endocrinologic and immunologic factors associated with recovery of growth in children with human immunodeficiency virus type 1 infection treated with protease inhibitors. *Pediatric Infectious Disease Journal*, *22*:70–76.

Watkins, J.M., Cool, V.A., Usner, D., Stehbens, J.A., Nichols, S., Loveland, K.A., Bordeaux, J.D., et al (2000). Attention in HIV-infected children: results from the Hemophilia Growth and Development Study. *Journal of the International Neuropsychology Society*, *6*:443-454.

Wechsler, S. (1995). *The semantic basis of argument structure*. CSLI Publications (Center for the Study of Language and Information). Stanford; New York: Cambridge University Press.

Woods, P.S., Iudicello, J.E., Moran L.M., Carey, C.L., Dawson, M.S., Grant, I. and The HIV Neurobehavioral Research Center (HNRC) (2008). HIV-associated Prospective Memory Impairment Increases Risk of Dependence in Everyday Functioning, *Neuropsychology*, *22*, 110–117