BMJ Open

THREE DECADE NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-007986
Article Type:	Research
Date Submitted by the Author:	16-Feb-2015
Complete List of Authors:	Heikinheimo, Terttu; Helsinki University Central Hospital, Neurology Poutiainen, Erja; University of Helsinki, Institute of Behavioral Sciences; Helsinki University Central Hospital, Salonen, Oili; Helsinki University Central Hospital, Department of Radiology Elovaara, Irina; University of Tampere, Neurology Ristola, Matti; Helsinki University Central Hospital, Infectious diseases
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Neurology, Infectious diseases
Keywords:	INFECTIOUS DISEASES, Dementia < NEUROLOGY, HIV & AIDS < INFECTIOUS DISEASES, Adult neurology < NEUROLOGY, Infectious disease/HIV < NEUROLOGY

SCHOLARONE™
Manuscripts

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

THREE DECADE NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY

Heikinheimo T[1], Poutiainen E[1,2], Salonen O[3], Elovaara I[4], Ristola M[5]

Correspondence to: [1]Dr. Terttu Heikinheimo, Department of Neurology, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00290, Helsinki, Finland.

Tel: + 358 9 4717 2662, Fax: +358 9 4717 4056

E-mail: terttu.heikinheimo-connell@hus.fi

[2]Rehabilitation Foundation, Helsinki, Finland.

[3]Department of Radiology, Helsinki University Central Hospital, Helsinki, Finland.

[4]Neuroimmunology Unit, Medical School, University of Tampere, Tampere, Finland.

[5]Department of Infectious Diseases at Aurora Hospital, Helsinki University Central Hospital, Helsinki, Finland

Key words: HIV, cognitive impairment, neuroAIDS, HAND

Tables: 2

References: 40

Word count: Abstract 250, Article 3098

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ABSTRACT

Background: How a very long-term HIV-infection affects neurological and neurocognitive functions? Our study-patients that have lived with HIV for decades were re-investigated.

Methods: This is an interventional follow-up study of HIV-infected cohort of patients. They were examined in three time periods: during the years 1986-1990, in 1997, and in 2013. They underwent neurological and neuropsychological examinations, magnetic resonance imaging of the brain and laboratory tests including the blood CD4-cells, plasma HIV-1 RNA. Neuropsychological examination included several measures: subtests of Wechsler Adult Intelligence Scale, Wechsler Memory Scale - revised , list learning, Stroop, and Trail-Making-B test. The Beck Depression Inventory, and Fatigue Severity Scale were done. The three examination time periods obtained data were compared with each other.

Results: Of the original 80 patients, 17 participated in all three examinations performed 1986-2013. The time from the HIV-diagnosis was 27(23 to 30) years. The blood CD4-cells at the diagnosis was 610(29 to 870)cells/mm3, and the nadir CD4 168 (4 to 408)cells/mm3. The time on combined antiretroviral treatment was 13(5 to 17) years.

Nine patients suffered from fatigue, five had polyneuropathy, and three had lacunar cerebral infarcts. There was a subtle increase of brain atrophy in two patients. Mild depressive symptoms were common. The neuropsychological follow-up showed typical age-related cognitive changes. No HIV-associated dementia features were detected.

Conclusions: Polyneuropathy, fatigue and mild depression were common but more severe neurological abnormalities were absent. These long-term surviving HIV-seropositive patients, while on best-available treatment, showed no evidence of HIV-associated neurocognitive disorder in neuropsychological and neuroradiological evaluations.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY: STRENGTHS OF THIS STUDY

- A very long term, meticulous follow-up of HIV infected patients.
- The study evaluated almost a half of the Finnish HIV population during 1986-1990.
- A systematic neuropsychological and neurological, neuroimaging and HIV infection assessment is included.

LIMITATIONS OF THIS STUDY

- A small study sample.
- Survival bias.

Extra data is available by emailing: Terttu.heikinheimo-connell@hus.fi

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

INTRODUCTION

Human immunodeficiency virus (HIV) has been challenging the mankind for more than 30 years. The virus crosses the blood-brain barrier (BBB) and enters the central nervous system (CNS) at the early stage of the infection - and never leaves it again. Without treatment HIV gradually causes a variety of neurological complications including HIV-associated neurocognitive disorder (HAND). This can vary from clinically asymptomatic or mild neurocognitive disorder to, when severest, HIV associated dementia (HAD). With the development of combined antiretroviral therapy (cART) patients with good adherence can live a long symptom-free life, and HAD has become rare,[1]. cART does not eliminate the virus, however, and it is claimed that a substantial portion of patients still develop neurocognitive impairments,[2-5]. Low level of cell-to-cell viral replication occurs also during the most successful cART-regimens,[6,7]. Even during effective cART there is a latent reservoir of blood CD4-cells carrying HIV-genome which is competent for replication,[8,9]. Low nadir CD4 seems to predict at least partially reversible HAND,[2]. A very long-term follow-up studies about the evolution of neurocognitive function among HIV infected patients are lacking. To our knowledge this is the first study describing a group of patients followed up to even 30 years.

Public health care provides HIV treatment in Finland. In Helsinki-area, the infectious disease unit at Aurora Hospital has given medical treatment for HIV infection since 1983,[10]. The first antiretroviral agent, zidovudine, became available at Aurora Hospital in 1987. A cohort study was started between 19865-1990 to examine the CNS-symptoms associated with HIV-infection,[11]. HIV-infected subjects were reinvestigated in 1997,[12]. In this study, in 2013, we re-invited the subjects with the purpose to obtain longitudinal evaluation of neurocognition, neurological and neuroimaging findings of a group of persons who became infected with HIV-1 more than 25 years ago and who have been treated with optimal therapy. In Finland antiviral HIV-medication is free for patients through the Finnish communicable disease legislation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

METHODS

Centre and patients

This is an interventional follow-up study of HIV infected patients who were first enrolled in the neurological and neuropsychological examination during the years 1986-1990,[13,14]. HIV-infection and AIDS are reportable diseases in Finland. The first patient with an HIV-infection was diagnosed 1983,[10]. The infectious disease unit at Aurora Hospital in Helsinki takes care of HIV-infected individuals within greater Helsinki area. The hospital managed a total of 98 HIV-infected patients in 1986. The amount of patient increased every year being 248 by the year 1991. Around half of these patients (n=106) were for the first time evaluated for this study during the years of 1986-1990. The exclusion criteria were: history of CNS-disease or present HIV-related CNS-disease (not HAD), severe dementia, marked learning disability, prominent alcohol consumption (scale 4, see below) and refusal of participation. Thus 85 patients participated the initial study,[13, 15]. Later, the subjects with previously diagnosed psychiatric problems, further 5 patients were excluded, thus the study cohort available for the follow-up included 80 persons. We have included in this analysis those patients who were re-invited and agreed to participate in all three study interventions in 1986-1990,[11], 1997,[12] and 2013.

Study interventions

During all three examination periods detailed medical history was taken together with information of educational background, profession and occupation. From each patient's medical records and previous research records, following data were recorded: dates of acquisition and diagnosis of HIV infection, history of the antiretroviral therapy, the start of cART and possible interruptions of the therapy. Virologically suppressive therapy was defined as having most plasma HIV viral loads below the limit of detection before the year 2000 and below 50 copies/mL thereafter. Blood CD4-cells (cells/mm^3) within the year from diagnosis and nadir CD4 (The lowest blood CD4-cells value

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

measured since patient's HIV diagnosis), date of plasma HIV-1 RNA-level being below 400 copies and below 50 copies, and any AIDS events were recorded. Patients were further divided in two groups depending on whether they had used cART for more than 10 years continuously versus subjects with less than 10 years of cART or treatment interruptions. In another dividing patients with low nadir CD4 (<200 cells/mm^3) to higher nadir CD4 values were compared.

Diagnosis of other conditions were recorded from the medical records and using information from the patient: Medication or diet used for diabetes mellitus, hypertension (treated, or a history of hypertension as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both), hypercholesterolemia (treated or total cholesterol level ≥5.0 mmol/L, low-density lipoprotein level ≥3.0 mmol/L, or high-density lipoprotein level <1.0 mmol/L), and cardiovascular disease (prior diagnosis of coronary heart disease or myocardial infarction (MI)). Diagnosis of nephropathy or signs of protein in urine were recorded. Any history of depression or bipolar disorder, diagnosis of epilepsy or dementia were asked. Patients were also asked about their smoking habits, and whether they used any illegitimate drugs. Alcohol consumption was estimated (scale 0-4) in first and last evaluations,[15]. In the scale, 0 means infrequent use (0-100g alcohol per week), 1 = social drinker (101-250 g), 2 = moderate user (251-350 g), 3 = heavy drinker (351-500 g) and 4 meaning alcohol abuser (>500 g). Body mass index was calculated for all the patients to estimate nutritional status (underweight BMI ≤ 18.5 kg/m²) and obesity (BMI ≥30 kg/m²).

Neurological Investigations.

In 2013, all the subjects filled up fatigue severity scale (FSS) translated to Finnish to determine the level of fatigue patients were experiencing,[16]. FSS has nine statements, scoring 1-7. Patient fills the scale based on how well the statement reflects his condition during the previous week. A total score ≥ 36 (max 63) in FSS suggests the patient is suffering from fatigue,[16].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

In the year 2013 assessment, diagnosis of polyneuropathy or treatment of neuropathic pain were recorded.

Each subject undervent neurological evaluation performed by a neurologist in all three time periods. In 2013, we used neurostatus scoring system and Expanded Disability Scale Status (EDSS),[17]. Neurostatus is divided in domains of visual, brainstem, pyramidal, cerebellar, sensory and bowel/bladder. The cerebral domain we excluded because of neuropsychological investigations with more detailed information. Each domain gives patient functional system score (FS) where 0-1 means no symptoms, signs only, 2-3 = mild symptoms and signs, 3 = moderate symptoms and signs, 4-6 = severe symptoms and signs. The domains are used to determine patients EDSS together with patient's ability to walk (ambulatory). Both neurostatus and EDSS are used widely to estimate the functional disability of patients with multiple sclerosis. Here it was adapted with the purpose to standardize the neurological status and to make the clinical neurological examination easier to analyse quantitatively.

Neuropsychological investigation

Neuropsychological examination included measures of memory: Logical Memory I of the Wechsler Memory Scale –Revised (WMS-R),[18], and a List learning task,[19]. Reasoning was assessed using Similarities and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS),[20]. Executive functions were assessed with the Trail Making B,[21] and the Interference subtask of the Stroop colour word test,[22]. Speed of performance was measured with Digit Symbol subtest of the WAIS and a naming subtest of the Stroop colour word test. Depression was evaluated with a short form of the Beck Depression Inventory (BDI),[23]. All subjects were investigated with same neuropsychological tests in all three study periods.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Neuroradiological investigation

MRI was performed to 16 patients both in years 1997 and 2013. First brain MRI was performed on 1.5 T unit (Siemens, Vision). MRI protocol included conventional T2, FLAIR, T2 coronal and T1 MPR sagittal images. Second imaging in the year 2013 was performed on 3 T unit (Philips, Achieva). MRI protocol included as well T2*, SWI and DWI axial sequences.

All brain abnormalities including infarcts and bleedings were recorded. The white matter hyperintensities (WMHIs) were classified as periventricular WMHIs or deep WMHIs and graded 0 through 3. The severity of white matter lesions (WMLs) was rated with the Fazekas' scale,[26]. Bicaudate ratios and the width on third ventricle were measured to estimate the brain atrophy.

Laboratory investigations

Apart of HIV-laboratory workout mentioned above, following laboratory assessment was made: Complete blood count, liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total bilirubin), kidney function (creatinine, protein in urine), plasma glucose and lipids (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL] and triglycerides), viral hepatitis serology (hepatitis B antigens [HBsAg, HBcAb], hepatitis C antigen [HCVAb] syphilis serology (treponema pallidum haemagglutination [TPHA] and cardiolipin antigens [VDRL])

Statistics

Statistical analyses were computed using IBM statistics software SPSS v.22.00. Neuropsychological parameters were analysed with multivariate analyses of variance (Manovas) controlling the effect of age in all analyses. In the analysis of other parameters simple parametric and nonparametric tests and simple descriptive statistics were used as appropriate.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Ethics

This research was approved by the medical ethical committee of the Hospital District of Helsinki and Uusimaa. All patients gave their written informed consent to participate the study.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

RESULTS

After exclusions the original study group consisted 80 patients during 1985-1990. By 1997 evaluation, 47 patients had passed away, 7 had been lost for follow-up and 3 patients refused the follow-up evaluation, so 23 patients were evaluated in 1997. Between 1997 and the current evaluation further five patients had passed away, two of them because of AIDS-related deaths after 1997 and three of them because of non-AIDS causes after four or more years after 1997. For the latest evaluation, we were able to contact 18 HIV-infected patients to participate in neurological, neuropsychological, radiological and laboratory work-up. The patients were all men. They had a sexually acquired HIV-infection, 16 through homo or bisexual contact and two through a heterosexual contact. All 18 patients gave their consent to participate in the study. One of them was too ill to participate in extended investigations and was only visited by the neurologists. His EDSS was 9.0. During the intervention in 2013 he passed away. No signs of HIV-associated brain damage were observed in post mortem autopsy. The results of the remaining 17 patients are reported here.

The demographic and clinical characteristics are presented in table 1. Out of the 17 patients, 11 (65 %) had had low nadir CD4 of < 200 cells/mm^3 and three (18 %) had had AIDS events. The median year of starting the first antiretroviral therapy was 1992 (range 1989 to 2002), Nine patients had had continuously virologically suppressive antiretroviral therapy for 10 years or longer. Remaining eight patients had had interruptions of suppressive antiretroviral therapy or had had continuously suppressive antiretroviral therapy for less than 10 years.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 1: Demographic and clinical characteristics of the study population. The number of patients (n) is 17 unless mentioned otherwise.

Charasteristic (unit)	Median	Range
Age / years	57.0	46-75
Education/years	12.0	9-23
HIV-infection[a]/ years n=16	28	23-31
HIV-diagnosis[b]/ years	27	23-30
CD4 at diagnosis[c] / cells/mm^3 n=15	610	29-870
nadir CD4 / cells/mm3	168	4-408
ARV / years	19	9-24
cART / years	13	5-17
BMI / kg/m^2	23.4	17.5-34.3
EDSS	2.0	1.0-4.0
FSS	32	9-63

[a] = patients own estimation about time from HIV-infection. [b] = time from the HIV-diagnosis. [c]= the first blood CD4 cells, within the year from the diagnosis. ARV = use of any antiretroviral therapy. cART = use of virologically suppressive antiretroviral therapy. BMI = body mass index, EDSS = Expanded disability status scale, FSS = Fatigue Status scale

Depression was diagnosed and treated in four (24 %) patients. In results of BDI, between the three study time periods no significant changes appeared: BDI mean scores were 4.65, 5.53 and 5.00, respectively (Friedman, Chi ^{2} = 0.5, p=0.779) indicating mild depressive symptoms. The BDI result did not vary between the groups of low nadir CD4 or patients with cART therapy for more than 10 years. Hypertension was medicated and treated in five (29 %) men. Diabetes was diagnosed in two subjects. Nephropathy was diagnosed in two patients, one caused by diabetes and the other by prostatic hyperplasia, and two subjects had protein in urine. Dyslipidemia was diagnosed in 11 (65%) of the patients. One patient was underweight (BMI 17.5 kg/m^2) and one obese (BMI 34.3

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

kg/m^2). Alcohol consumption has been moderate and reduced significantly between the first and last examination (mean score±SD: 0.82±.0.64 vs. 0.35 ± 0.79, Wilcoxon, Z = -2.3, p = 0.021).

Tobacco smoking was a habit of 7 (41 %) patients. One patient told he occasionally used marihuana. None of the subjects used iv-drugs or other illegitimate drugs.

Four of the patients had a diagnosis of neuropathy. On the clinical neurological examination an additional patient had signs of neuropathy (Sensory FS 3.0-4.0). Altogether 6 patients had EDSS between 3.0 and 4.0 (mean = 3.4) indicating moderate disability. In five of them this was due to neuropathy. One patient had mild extrapyramidal findings and bladder dysfunction that increased his EDSS. None of the patients had prominent loss of vision, cerebellar ataxia, marked pyramidal symptoms or other clear signs of central nervous system abnormalities. They were all fully ambulatory. Most of the patients (16) had intact sensation of smell.

Neuropsychological examination showed mild decline in raw scores but no significant changes were found when age was controlled in statistical analyses (Table 2). Neither being on cART for at least 10 years continuously versus for less than 10 years or having an interruption of cART nor low nadir CD4 had any effect on cognitive change during the follow-up.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 2. Cognitive functioning of the 17 HIV infected patients at 3 follow-up examinations.

Year of examination	**1986-90**	**1997**	**2013**	**Manova***		**Effectsize**
Follow-up time/years	**0**	**7-11**	**23-27**			
	mean (sd)*	mean (sd)	Mean (sd)	F	P value	Eta Square
Cognitive function						
Memory				1.920	0.172	0.390
WMS Logical memory	11.9 (2.1)	13.8 (2.5)	10.0 (2.6)	-	-	-
List learning	57.9 (6.2)	61.9 (5.4)	57.3 (7.4)	-	-	-
Reasoning				0.895	0.496	0.230
WAIS Similarities	21.9 (1.7)	21.3 (1.8)	20.9 (2.0)	-	-	-
WAIS Block Design	40.9 (6.5)	41.5 (5.3)	37.9 (6.1)	-	-	-
Executive function				0.330	0.953	0.099
Trail-Making B	85.3 (21.5)	99.4 (29.8)	105.9 (27.2)	-	-	-
Stroop Interference test (time)	104.2 (24.8)	99.2 (22.6)	115.5 (34.8)	-	-	-
Speed of performance				1.221	0.353	0.289
WAIS Digit Symbol	59.3 (11.0)	55.4 (16.8)	48.9 (12.7)	-	-	-
Stroop Naming (time)	55.4 (11.6)	57.0 (11.4)	67.4 (15.7)	-	-	-

* raw scores

The neuroradiological follow-up showed only minimal age-related increasing in atrophic changes. The mean bicaudate ratio was 0,12 in 1997 and 0,13 in 2013, respectively the mean width of on third ventricle was 0,57 cm and 0,68 cm. Two of the patients showed slightly more prominent increase in atrophy. Three of the patients had new lacunar infarcts, one of them seen one already in 1997. One of them had as well microhemorrhages not seen in 1997. Four patients had new WMHIs. One of the three patients with strokes was the eldest (75-year-old) of our study group and had some decline in his neuropsychological performance. However, the other patients with mild brain atrophy or stroke in MRI had no detectable decline in cognitive performance.

Five patients had positive HBcAb indicating an earlier hepatitis B infection, but none of them was HBsAg positive, so none of the patients were chronically infected with hepatitis B. One patient had positive syphilis serology with a history and a serological follow-up of an adequate treatment of syphilis.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only

DISCUSSION

This study shows for the first time that HIV-1 infected patients who receive adequate anti-HIV therapy may preserve their neurological and neurocognitive function well despite of a history of HIV infection up to 30 years.

All cART-medication regimes are reducing the risk of the severest forms of HAND but, however, the milder forms have been reported to become more common,[25,26]. HIV is transported from periphery through BBB in the CNS with both monocytes and CD4 cells,[27,28]. In the CNS the monocytes transfer HIV into macrophages and microglial cells both of which can produce HIV virions. HIV infection may be either hematogenous, "autonomous" when viral replication takes place in the CNS or a mixture of both,[27]. Astrocytes also become infected with HIV, but HIV does not replicate in astrocytes. The infected macrophages and microglial cells elicit an inflammatory reaction. This recruits more infected immune cells in the brain,[28]. Also astrocytes contribute to the damage of brain by producing neurotoxic factors, like glutamate,[25,26]. The only known therapy to reduce the CNS damage by HIV is ART. Even a monotherapy with zidovudine decreases the amount of inflammatory reaction in the cerebrospinal fluid (CSF),[29]. The modern cART regimens inhibit the replication of HIV almost completely in the periphery. These regimens have shown to reduce HIV viral load to undetectable level in the CNS in most patients,[30]. The inflammation markers in the CSF may persist at an elevated level, however, even after four years of virologically successful cART,[31]. Our results indicate that cognitive function can be preserved in HIV-infected patients for a couple of decades despite the probable inflammatory activity in the CNS.

It is described that some HIV-infected patients have a viral escape of HIV in the CNS in spite of a successful cART in the periphery,[32]. The phenomenon is fairly rare affecting a minority of patients receiving a successful cART. It appears from the brain MRI results that our cohort did not

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

include such persons. The factors contributing to the good cognitive state in our patients probably include, first, a long-term ART which on the average had been 19 years of which on the average 13 years had been on cART. Second, lack of drug abuse which is perhaps synergistic with HIV to cause HAND. The CHARTER study recruited 1555 HIV-infected subjects across the USA and found that 52 % of them had at least mild neuropsychological impairment,[2]. In this study sample about a third (28 %) were using some recreational drugs. Third, the good neurocognitive outcome is caused most likely by biological variation in our patients' properties to resist HIV infection, and their willingness to start ART. Last, lack of hepatitis C infection may contribute to the good neurocognitive outcome of our patients,[33, 34].

The only significant neurological impairment detected in our study population was peripheral neuropathy. Apart from one patient with extrapyramidal signs, no signs of other central nervous system impairment were found in clinical examination. The earlier ART has probably contributed to the development of neuropathy, because many patients had used deoksinucleoside analogues, which are known to cause toxic neuropathy, as a part of their ART.

A great proportion of our patients had diseases that constitute risks for cerebrovascular diseases. However, the only risk factor that was significantly higher than in general population of Finland, was expectedly the prevalence of hypercholesterolemia. This is a well-known side effect of cART, especially the group of protease inhibitors,[35, 36]. Diabetes, hypertension and hypercholesterolemia were treated appropriately which also decreased the risks for neurological and neurocognitive defects.

In MRI the signs of silent strokes support the research, which shows increase of incidence of stroke in the aging HIV-population,[37,38]. Only two of our patients had developed brain tissue atrophy that was more significant than in normal aging, annually 0.1-0.3 % in men,[39,40].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only

Limitations of the study include survival benefit and small sample size. It may well be that our population of survivors from the era when anti-HIV medication was not available or did not give a long-term suppression of HIV-1 replication represent a subgroup of HIV infected persons who tolerate the infection better that men in the average. On the other hand, the recruited study group represents almost a half of the HIV-infected persons treated in Aurora Hospital during 1980s.

In conclusion our results give credence to the view that HIV-1 infected persons may preserve well their neurocognitive function when cART is started in time and delivered well and other conditions that may threaten the brain are treated appropriately. Apart from polyneuropathy, no significant neurological or neuropsychological trend of impairment were found in our study group. It is possible that the prevalence of neurocognitive impairment in the CHARTER study may not apply to all HIV-1 infected populations.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ACKNOWLEDGEMENTS

The authors thank Outi Debnam, RN, for practical assistance in conducting this study.

COMPETING INTERESTS

Terttu Heikinheimo: travel expenses from Abbvie, Bayer and Orion.

Erja Poutiainen: travel expenses and consultations from AbbVie

Oili Salonen: no interests

Irina Elovaara: no interests.

Matti Ristola: Honoraria, consultations, or travel expenses from Abbvie, BMS, Gilead, GSK, Janssen, and Merck. Grants for scientific activities from AbbVie and GSK.

FUNDING STATEMENT

This work was supported by an unrestricted research grant for the intervention in 2013 through the Clinical Research Institute of HUCH by AbbVie. Terttu Heikinheimo received support from Helsinki University Hospital research funds, Maire Taponen foundation and Orion research funds.

CONTRIBUTORSHIP STATEMENT

All authors included on a paper fulfil the four criteria of authorship according to ICMJE recommendation, TH is the corresponding author. In addition EP and IE collected the original data and the evaluations during 1986-1990 and year 1997. EP and TH produced the statistical data, OS analysed the MRI images from 1997 and 2013. MR evaluated HIV infection in 1997 and 2013, and organised the evaluation of the cohort in 2013. EP did the neuropsychological and TH the neurological assessment.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

REFERENCES

[1] Monforte A, Cinque P, Mocroft A, *et al*. Changing Incidence of Central Nervous System Diseases in the EuroSIDA Cohort. *Annals of Neurology* 2004;**55**:320-328.

[2] Heaton RK, Clifford DB, Franklin DR,Jr, *et al*. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 2010;**75**(23). doi:10.1212/WNL.0b013e318200d727; 10.1212/WNL.0b013e318200d727.

[3] Heaton RK, Franklin DR, Ellis RJ, *et al*. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 2011;**17**(1). doi:10.1007/s13365-010-0006-1; 10.1007/s13365-010-0006-1.

[4] Simioni S, Cavassini M, Annoni JM, *et al*. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010;**24**(9). doi:10.1097/QAD.0b013e3283354a7b; 10.1097/QAD.0b013e3283354a7b.

[5] Ances BM, Clifford DB. HIV-associated neurocognitive disorders and the impact of combination antiretroviral therapies. *Curr Neurol Neurosci Rep* 2008;**8**(6).

[6] Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. *Nat Rev Immunol* 2005;**5**(1). doi:10.1038/nri1527.

[7] Sattentau QJ. Cell-to-Cell Spread of Retroviruses. *Viruses* 2010;**2**(6). doi:10.3390/v2061306 [doi].

[8] Eriksson S, Graf EH, Dahl V, *et al*. Comparative analysis of measures of viral reservoirs in HIV-1 eradication studies. *PLoS Pathog* 2013;**9**(2). doi:10.1371/journal.ppat.1003174 [doi].

[9] Pierson T, McArthur J, Siliciano RF. Reservoirs for HIV-1: mechanisms for viral persistence in the presence of antiviral immune responses and antiretroviral therapy. *Annu Rev Immunol* 2000;**18**. doi:18/1/665 [pii].

[10] Kivela PS, Krol A, Salminen MO, *et al*. Determinants of late HIV diagnosis among different transmission groups in Finland from 1985 to 2005. *HIV Med* 2010;**11**(6). doi:10.1111/j.1468-1293.2009.00783.x; 10.1111/j.1468-1293.2009.00783.x.

[11] Poutiainen E, Elovaara I, Raininko R, *et al*. Cognitive decline in patients with symptomatic HIV-1 infection. No decline in asymptomatic infection. *Acta Neurol Scand* 1996;**93**(6).

[12] Poutiainen E, Elovaara I, Salonen O, *et al*. Cognitive performance and brain atrophy in the long term follow-up of HIV-1-infected patients [abstract]. *22nd International Neuropsychological Society Mid-Year Conference* 1999.

[13] Poutiainen E. Cognitive deficits and emotional disorders in HIV-1 infected individuals. *Acta Psychiatr Scand* 1995;**92**(6).

[14] Poutiainen E, Elovaara I, Raininko R, *et al*. Cognitive performance in HIV-1 infection: relationship to severity of disease and brain atrophy. *Acta Neurol Scand* 1993;**87**(2).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

[15] Poutiainen E, Elovaara I. Subjective complaints of cognitive symptoms are related to psychometric findings of memory deficits in patients with HIV-1 infection. *J Int Neuropsychol Soc* 1996;**2**(3).

[16] Krupp LB, LaRocca NG, Muir-Nash J*, et al*. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;**46**(10).

[17] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**(11).

[18] Wechsler D. *Manual for the Wechsler Memory Scale-Revised.*. San Antonio, Texas: The Psychological Corporation 1987.

[19] Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th Ed. New York: Oxford University Press, 2004.

[20] Wechsler D. Wechsler adult intelligence scale. Manual. New York: The Psychological Corporation, 1955.

[21] Army Individual Test Battery. Manual of directions and scoring. 1944;.

[22] Stroop JR. Studies in interference in serial verbal reactions. *Journal of Experimental Psychology* 1935; **18**, 643-662.

[23] Beck AT, Beck RW. Screening depressed patients in family practice. A rapid technic. *Postgrad Med* 1972;**52**(6).

[24] Fazekas F, Chawluk JB, Alavi A*, et al*. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987;**149**(2). doi:10.2214/ajr.149.2.351 [doi].

[25] Chan P, Brew BJ. HIV Associated Neurocognitive Disorders in the Modern Antiviral Treatment Era: Prevalence, Characteristics, Biomarkers, and Effects of Treatment. *Curr HIV/AIDS Rep* 2014;. doi:10.1007/s11904-014-0221-0 [doi].

[26] Brew BJ, Chan P. Update on HIV Dementia and HIV-Associated Neurocognitive Disorders. *Curr Neurol Neurosci Rep* 2014;**14**(8). doi:10.1007/s11910-014-0468-2 [doi].

[27] Spudich SS, Nilsson AC, Lollo ND*, et al*. Cerebrospinal fluid HIV infection and pleocytosis: relation to systemic infection and antiretroviral treatment. *BMC Infect Dis* 2005;**5**. doi:1471-2334-5-98 [pii].

[28] Kraft-Terry SD, Stothert AR, Buch S*, et al*. HIV-1 neuroimmunity in the era of antiretroviral therapy. *Neurobiol Dis* 2010;**37**(3). doi:10.1016/j.nbd.2009.12.015 [doi].

[29] Elovaara I, Poutiainen E, Lahdevirta J*, et al*. Zidovudine reduces intrathecal immunoactivation in patients with early human immunodeficiency virus type 1 infection. *Arch Neurol* 1994;**51**(9).

[30] Robertson KR, Robertson WT, Ford S*, et al*. Highly active antiretroviral therapy improves neurocognitive functioning. *J Acquir Immune Defic Syndr* 2004;**36**(1). doi:00126334-200405010-00003 [pii].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

[31] Yilmaz A, Price RW, Gisslen M. Antiretroviral drug treatment of CNS HIV-1 infection. *J Antimicrob Chemother* 2012;**67**(2). doi:10.1093/jac/dkr492 [doi].

[32] Eden A, Fuchs D, Hagberg L, *et al*. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis* 2010;**202**(12). doi:10.1086/657342 [doi].

[33] Vivithanaporn P, Nelles K, DeBlock L, *et al*. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *J Neurol Sci* 2012;**312**(1-2). doi:10.1016/j.jns.2011.08.025 [doi].

[34] Devlin KN, Gongvatana A, Clark US, *et al*. Neurocognitive effects of HIV, hepatitis C, and substance use history. *J Int Neuropsychol Soc* 2012;**18**(1). doi:10.1017/S1355617711001408 [doi].

[35] Penzak SR, Chuck SK. Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment. *Scand J Infect Dis* 2000;**32**(2).

[36] Muronya W, Sanga E, Talama G, *et al*. Cardiovascular risk factors in adult Malawians on long-term antiretroviral therapy. *Trans R Soc Trop Med Hyg* 2011;**105**(11). doi:10.1016/j.trstmh.2011.07.016; 10.1016/j.trstmh.2011.07.016.

[37] Benjamin LA, Bryer A, Emsley HC, *et al*. HIV infection and stroke: current perspectives and future directions. *Lancet Neurol* 2012;**11**(10). doi:10.1016/S1474-4422(12)70205-3; 10.1016/S1474-4422(12)70205-3.

[38] Chow FC, Regan S, Feske S, *et al*. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr* 2012;**60**(4) (accessed 20120709). doi: http://dx.doi.org/10.1097/QAI.0b013e31825c7f24.

[39] Xu J, Kobayashi S, Yamaguchi S, *et a*l. Gender effects on age-related changes in brain structure. *AJNR Am J Neuroradiol* 2000;**2**1(1).

[40] Ge Y, Grossman RI, Babb JS, *et a*l. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. *AJNR Am J Neuroradiol* 2002;**2**3(8).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Research Checklist

THREE DECADE NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page	Item No	Recommendation
Title and abstract	2	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	2		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	4	2	Explain the scientific background and rationale for the investigation being reported
Objectives	4	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	5	4	Present key elements of study design early in the paper
Setting	5	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
	–		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	5-8	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	5-8	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	-	9	Describe any efforts to address potential sources of bias
Study size	5	10	Explain how the study size was arrived at

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Quantitative variables		11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	8	12	(*a*) Describe all statistical methods, including those used to control for confounding
			(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) If applicable, explain how loss to follow-up was addressed
			(*e*) Describe any sensitivity analyses
Results			
Participants	9	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	9		(b) Give reasons for non-participation at each stage
	-		(c) Consider use of a flow diagram
Descriptive data	9,10	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	10		(b) Indicate number of participants with missing data for each variable of interest
	12		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	-	15*	Report numbers of outcome events or summary measures over time
Main results	10-12	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
	-		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses		17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only

Key results	14	18	Summarise key results with reference to study objectives
Limitations	16	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	14-15	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	16	21	Discuss the generalisability (external validity) of the study results
Other information			
Funding	17	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

THREE DECADES NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-007986.R1
Article Type:	Research
Date Submitted by the Author:	04-Sep-2015
Complete List of Authors:	Heikinheimo, Terttu; Helsinki University Central Hospital, Neurology Poutiainen, Erja; University of Helsinki, Institute of Behavioral Sciences; Helsinki University Central Hospital, Salonen, Oili; Helsinki University Central Hospital, Department of Radiology Elovaara, Irina; University of Tampere, Neurology Ristola, Matti; Helsinki University Central Hospital, Infectious diseases
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Neurology, Infectious diseases
Keywords:	INFECTIOUS DISEASES, Dementia < NEUROLOGY, HIV & AIDS < INFECTIOUS DISEASES, Adult neurology < NEUROLOGY, Infectious disease/HIV < NEUROLOGY

SCHOLARONE™
Manuscripts

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

THREE DECADES NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY

Heikinheimo T[1], Poutiainen E[1,2], Salonen O[3], Elovaara I[4], Ristola M[5]

Correspondence to: [1]Dr. Terttu Heikinheimo, Department of Neurology, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00290, Helsinki, Finland.

Tel: + 358 9 4717 2662, Fax: +358 9 4717 4056

E-mail: terttu.heikinheimo-connell@hus.fi

[2]Rehabilitation Foundation, Helsinki, Finland.

[3]Department of Radiology, Helsinki University Central Hospital, Helsinki, Finland.

[4]Neuroimmunology Unit, Medical School, University of Tampere, Tampere, Finland.

[5]Department of Infectious Diseases at Aurora Hospital, Helsinki University Central Hospital, Helsinki, Finland

Key words: HIV, cognitive impairment, neuroAIDS, HAND

Tables: 4

References: 40

Word count: Abstract 300, Article 3393 (not including tables).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ABSTRACT

Objectives: Is it possible to live without any neurocognitive or neurological symptoms, when being infected with HIV for a very long time? These study-patients with decades long HIV infection were observed in this follow-up study in three time periods: 1986-1990, in 1997 and in 2013.

Setting: The patients from greater Helsinki area were selected from outpatients' unit of infectious diseases.

Participants: The study included 80 HIV-patients. Patients with heavy alcohol consumption, central nervous system disorder or psychiatric disease were excluded. Due to high mortality, only 17 male patients participated all three time periods.

Primary and secondary outcome measures: The patients underwent neurological and neuropsychological examinations, magnetic resonance imaging of the brain and laboratory tests including the blood CD4-cells, plasma HIV-1 RNA. Neuropsychological examination included several measures: subtests of Wechsler Adult Intelligence Scale, Wechsler Memory Scale-Revised, list learning, Stroop, and Trail-Making-B test. The Beck Depression Inventory, and Fatigue Severity Scale were done. The obtained data from the three time periods were compared with each other.

Results: Of the original 80 patients, 17 participated in all three examinations performed 1986-2013. The time from the HIV-diagnosis was 27 (23 to 30) years. The blood CD4-cells at the diagnosis were 610 (29 to 870)cells/mm3, and the nadir CD4 168 (4 to 408)cells/mm3. The time on combined antiretroviral treatment was 13 (5 to 17) years.

Nine patients suffered from fatigue, five had polyneuropathy, and three had lacunar cerebral infarcts. There was a subtle increase of brain atrophy in two patients. Mild depressive symptoms were common. The neuropsychological follow-up showed typical age-related cognitive changes. No HIV-associated dementia features were detected.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Conclusions: Polyneuropathy, fatigue and mild depression were common but more severe neurological abnormalities were absent. These long-term surviving HIV-seropositive patients, while on best-available treatment, showed no evidence of HIV-associated neurocognitive disorder in neuropsychological and neuroradiological evaluations.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ARTICLE SUMMARY: STRENGTHS OF THIS STUDY

- A very long term, meticulous follow-up of HIV infected patients.
- The study evaluated almost a half of the Finnish HIV population during 1986-1990.
- A systematic neuropsychological and neurological, neuroimaging and HIV infection assessment is included.

LIMITATIONS OF THIS STUDY

- A small study sample.
- Survival bias.

Extra data is available by emailing: Terttu.heikinheimo-connell@hus.fi

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

INTRODUCTION

Human immunodeficiency virus (HIV) has been challenging the mankind for more than 30 years. The virus crosses the blood-brain barrier (BBB) and enters the central nervous system (CNS) at the early stage of the infection - and never leaves it again. Without treatment HIV gradually causes a variety of neurological complications including HIV-associated neurocognitive disorder (HAND). This can vary from clinically asymptomatic or mild neurocognitive disorder to, when severest, HIV associated dementia (HAD). With the development of combined antiretroviral therapy (cART) patients with good adherence can live a long symptom-free life, and HAD has become rare,[1]. cART does not eliminate the virus, however, and it is claimed that a substantial portion of patients still develop neurocognitive impairments,[2-5]. A low level of cell-to-cell viral replication occurs also during the most successful cART-regimens,[6,7]. Even during effective cART there is a latent reservoir of blood CD4-cells carrying the HIV-genome, which is competent for replication,[8,9]. Low nadir CD4 seems to predict at least partially reversible HAND,[2]. Very long-term follow-up studies about the evolution of neurocognitive function among HIV infected patients are lacking. To our knowledge this is the first study describing a group of patients followed up even to 30 years.

Public health care provides HIV treatment in Finland. In the Helsinki-area, the infectious disease unit at Aurora Hospital has provided medical treatment for HIV infection since 1983,[10]. The first antiretroviral agent, zidovudine, became available at Aurora Hospital in 1987. A cohort study was started 1986 lasting five years to examine the CNS-symptoms associated with HIV infection,[11]. The HIV infected subjects were then reinvestigated in 1997,[12]. For this study we re-invited the subjects in 2013 with the purpose of obtaining a longitudinal evaluation of neurocognition, and the neurological and neuroimaging findings of a group of persons who became infected with HIV-1 more than 25 years ago, and who have been treated with optimal therapy. In Finland antiviral HIV-medication is free for patients through the Finnish communicable disease legislation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

METHODS

Centre and patients

This is an observational follow-up study of HIV infected patients who were first enrolled in the neurological and neuropsychological examination during the years 1986-1990,[13,14]. HIV infection and AIDS are reportable diseases in Finland. The first patient with an HIV infection was diagnosed in 1983,[10]. The infectious disease unit at Aurora Hospital in Helsinki takes care of HIV infected individuals within the greater Helsinki area. The hospital managed a total of 98 HIV infected patients in 1986. The number of patients increased every year to 248 by the year 1991. Around half of these patients (n=106) were for the first time evaluated for this study during the years of 1986-1990. The exclusion criteria were: history of CNS-disease or present HIV-related CNS-disease (not HAD), severe dementia, marked learning disability, prominent alcohol consumption (scale 4, see below) and refusal of participation. Thus, 85 patients participated in the initial study,[13, 15]. Later, the subjects with previously diagnosed psychiatric problems; a further 5 patients were excluded. Thus the study cohort available for the follow-up totalled 80 persons. We have included in this analysis those patients who were re-invited and agreed to participate in all three study interventions in 1986-1990,[11], 1997,[12], and 2013.

Study interventions

During all three examination periods the detailed medical history was taken together with information on their educational background, profession and occupation. From each patient's medical records and previous research records, the following data were recorded: dates of acquisition and diagnosis of HIV infection, the history of the antiretroviral therapy, and the start of cART and possible interruptions of the therapy. Virologically suppressive therapy was defined as having most plasma HIV viral loads below the limit of detection before the year 2000 and below 50 copies/mL thereafter. Blood CD4-cells (cells/mm^3) within the year from diagnosis and nadir CD4

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

(The lowest blood CD4-cells value measured since patient's HIV diagnosis), the date of plasma HIV-1 RNA level being below 400 copies and below 50 copies, and any AIDS events were recorded. Patients were further divided into two groups depending on whether they had used cART for more than 10 years continuously versus patients with less than 10 years of cART, or treatment interruptions. In another dividing patients with low nadir CD4 (<200 cells/mm^3) to higher nadir CD4 values were compared.

The diagnosis of other conditions were recorded from the medical records, and using information from the patient: medication or diet used for diabetes mellitus, hypertension (treated, or a history of hypertension as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both), hypercholesterolemia (treated or total cholesterol level ≥5.0 mmol/L, low-density lipoprotein level ≥3.0 mmol/L, or high-density lipoprotein level <1.0 mmol/L), and cardiovascular disease (prior diagnosis of coronary heart disease or myocardial infarction (MI)). Diagnosis of nephropathy or signs of protein in urine were recorded. Any history of depression or bipolar disorder, diagnosis of epilepsy or dementia was asked. Patients were also questioned about their smoking habits, and whether they used any illegitimate drugs. Alcohol consumption was estimated (scale 0-4) in the first and last evaluations,[15]. In the scale, 0 means infrequent use (0-100g alcohol per week), 1 = social drinker (101-250 g), 2 = moderate user (251-350 g), 3 = heavy drinker (351-500 g), and 4 meaning alcohol abuser (>500 g). The body mass index was calculated for all patients to estimate their nutritional status (underweight BMI ≤ 18.5 kg/m²) and obesity (BMI ≥30 kg/m²).

Neurological Investigations.

In 2013, all the subjects completed a fatigue severity scale (FSS) form translated in to Finnish to determine the level of fatigue patients were experiencing,[16]. The FSS has nine statements with a score range of 1-7. The patient accords a value based on how well the statement reflects his

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

condition during the previous week. A total score ≥ 36 (max 63) in the FSS suggests the patient is suffering from fatigue,[16].

In the year 2013 assessment, the diagnosis of polyneuropathy or treatment of neuropathic pain were recorded.

Each subject underwent a neurological evaluation performed by a neurologist in all three time periods. In 2013, we used a neurostatus scoring system and the Expanded Disability Scale Status (EDSS),[17]. The neurostatus is divided in to the domains of visual, brainstem, pyramidal, cerebellar, sensory and bowel/bladder. We excluded the cerebral domain, because we undertook neuropsychological investigations with more detailed information. Each domain gives the patient a functional system score (FS) where 0-1 means no symptoms, signs only; 2-3 = mild symptoms and signs; 3 = moderate symptoms and signs; 4-6 = severe symptoms and signs. The domains are used to determine patients EDSS together with patient's ability to walk (ambulatory). Both the neurostatus and EDSS are used widely to estimate the functional disability of patients with multiple sclerosis. For this study they were adapted with the purpose to standardizing the neurological status and making the clinical neurological examination easier to analyse quantitatively.

Neuropsychological investigation

The neuropsychological examination included measures of memory: the Logical Memory I of the Wechsler Memory Scale –Revised (WMS-R),[18], and a list learning task,[19]. The reasoning was assessed using Similarities and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS),[20]. The executive functions were assessed with the Trail Making B,[21] and the Interference subtask of the Stroop colour word test,[22]. The speed of performance was measured with the Digit Symbol subtest of the WAIS and a naming subtest of the Stroop colour word test. Depression was evaluated with a short form of the Beck Depression Inventory (BDI),[23]. All subjects were investigated with the same neuropsychological tests in all three study periods

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Neuroradiological investigation

MRI was performed on 16 patients both in years 1997 and 2013. The first brain MRI was performed using the 1.5 T unit (Siemens, Vision). The MRI protocol included conventional T2, FLAIR, T2 coronal and T1 MPR sagittal images. The second imaging in the year 2013 was performed using the 3 T unit (Philips, Achieva). The MRI protocol included as well the T2*, SWI and DWI axial sequences.

All brain abnormalities including infarcts and bleedings were recorded. The white matter hyperintensities (WMHIs) were classified as periventricular WMHIs or deep WMHIs, and graded 0 through 3. The severity of white matter lesions (WMLs) was rated with the Fazekas scale,[24]. The bicaudate ratios and the width on the third ventricle were measured to estimate the brain atrophy.

Laboratory investigations

Apart from the HIV laboratory workout mentioned above, the following laboratory assessment was made: a complete blood count, liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total bilirubin), kidney function (creatinine, protein in urine), plasma glucose and lipids (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL] and triglycerides), viral hepatitis serology (hepatitis B antigens [HBsAg, HBcAb], hepatitis C antigen [HCVAb], syphilis serology (treponema pallidum haemagglutination [TPHA] and cardiolipin antigens [VDRL]).

A current cerebrospinal fluid (CSF) sample was available of nine subjects for routine analysis.

Statistics

Statistical analyses were computed using IBM statistics software SPSS v.22.00. The neuropsychological parameters were analysed with multivariate analyses of variance (Manovas)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

controlling the effect of age in all analyses. In the analysis of other parameters simple parametric and nonparametric tests, and simple descriptive statistics were used as appropriate.

Ethics

This research was approved by the medical ethical committee of the Hospital District of Helsinki and Uusimaa. All patients gave their written informed consent to participate in the study.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

RESULTS

After exclusions the original study group consisted of 80 patients during the period 1986-1990. By 1997 evaluation, 47 patients had passed away, 7 had been lost for the follow-up, and 3 patients refused the follow-up evaluation, and consequently 23 patients were evaluated in 1997. Between 1997 and the current evaluation a further five patients had passed away, two of them because of AIDS-related deaths after 1997, and three of them because of non-AIDS related causes four or more years after 1997. For the latest evaluation, we were able to contact 18 HIV infected patients to participate in the neurological, neuropsychological, radiological and laboratory work-up. The patients were all men. They had a sexually acquired HIV infection, 16 through homo or bisexual contact and two through a heterosexual contact. All 18 patients gave their consent to participate in the study. One of them was too ill to participate in extended investigations and was only visited by the neurologists. His EDSS was 9.0. During the intervention in 2013 he died. No signs of HIV-associated brain damage were observed in post mortem autopsy. The results of the remaining 17 patients are reported here.

The demographic and clinical characteristics are presented in table 1. Out of the 17 patients, 11 (65 %) had had low nadir CD4 of < 200 cells/mm^3, and three (18 %) had had AIDS events (one patient with oesophageal candida, one with Pneumocystis pneumonia, and one with Kaposi's sarcoma and Pneumocystis pneumonia. The patient with two AIDS illnesses had had convulsions twice while receiving treatment Pneumocystis pneumonia). There were no elite controllers of HIV-1 viraemia among the subjects, whose median of the maximal HIV-1 viral load in plasma was 145000 copies/ml (range 10900 to 9360000 copies/ml). The median year of starting the first antiretroviral therapy was 1992 (range 1989 to 2002). Nine patients had had continuously virologically suppressive antiretroviral therapy for 10 years or longer. The remaining eight patients had had interruptions of suppressive antiretroviral therapy or had had continuously suppressive antiretroviral therapy for less than 10 years. The current antiretroviral combinations are shown in Table 2.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 1: Demographic and clinical characteristics of the study population. The number of patients (n) is 17 unless mentioned otherwise.

Charasteristic (unit)	Median	Range
Age / years	57.0	46-75
Education/ years	12.0	9-23
HIV infection[a]/ years n=16	28	23-31
HIV-diagnosis[b]/ years	27	23-30
CD4 at diagnosis[c] / cells/mm^3 n=15	610	29-870
nadir CD4 / cells/mm3	168	4-408
ARV / years	19	9-24
cART / years	13	5-17
BMI / kg/m^2	23.4	17.5-34.3
EDSS	2.0	1.0-4.0
FSS	32	9-63

[a] = patients own estimation about time from HIV infection. [b] = time from the HIV-diagnosis. [c]= the first blood CD4 cells, within the year from the diagnosis. ARV = use of any antiretroviral therapy. cART = antiretroviral therapy consisting of at least 3 agents. BMI = body mass index, EDSS = Expanded disability status scale, FSS = Fatigue Status scale

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 2: Current cART-regimens of 17 HIV infected patients.

cART-regime	Number of patients	Remarks
2NRTI+boosted PI	7	
2NRTI+NNRTI	3	
2NRTI+INSTI	1	
1NRTI+boostedPI+INSTI	1	intolerance to NRTI's
1NRTI+boostedPI+NNRTI	1	1 class ART resistance
NNRTI+boostedPI+INSTI	2	2 class ART resistance in both patients
2NRTI+boostedPI+NNRTI+INSTI	2	3 class ART resistance in both patients

NNRTI= non-nucleoside reverse transcriptase inhibitor, 2NRTI = two nucleoside reverse transcriptase inhibitors, PI = protease inhibitor, INSTI = integrase strand transfer inhibitor

Depression was diagnosed and treated in four (24 %) patients. In the results of BDI, between the three study time periods no significant changes appeared: BDI mean scores were 4.65, 5.53 and 5.00, respectively (Friedman, Chi ^{2} = 0.5, p=0.779) indicating mild depressive symptoms. The BDI result did not vary between the groups of low nadir CD4 or patients with cART therapy for more than 10 years. Hypertension was medicated and treated in five (29 %) men. Diabetes was diagnosed in two subjects. Nephropathy was diagnosed in two patients; one caused by diabetes and the other by prostatic hyperplasia, while two other subjects had protein in urine. Dyslipidemia was diagnosed in 11 (65%) of the patients. One patient was underweight (BMI 17.5 kg/m^2) and one obese (BMI 34.3 kg/m^2). Alcohol consumption has been moderate and was reduced significantly between the first and last examination (mean score±SD: 0.82±.0.64 vs. 0.35 ± 0.79, Wilcoxon, Z = -2.3, p = 0.021).

Tobacco smoking was a habit of 7 (41 %) patients. One patient informed that he occasionally used marihuana. None of the subjects used iv-drugs or other illegitimate drugs.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Four of the patients had a diagnosis of neuropathy. On clinical neurological examination an additional patient had signs of neuropathy (Sensory FS 3.0-4.0). Four of 5 patients with neuropathy had been treated with deoxynucleosides, 4 with stavudine from 3 to 10 years, and 3 with didanosine from 3 to 4.5 years. Only one patient with neuropathy had not been treated with deoxynucleosides. Altogether 6 patients had EDSS between 3.0 and 4.0 (mean = 3.4) indicating moderate disability. In five of them this was due to neuropathy. One patient had mild extrapyramidal findings and bladder dysfunction that increased his EDSS. None of the patients had prominent loss of vision, cerebellar ataxia, marked pyramidal symptoms or other clear signs of central nervous system abnormalities. They were all fully ambulatory. Most of the patients (16) had intact sensation of smell.

The neuropsychological examination showed a mild decline in raw scores particularly between the second and last examination, but no significant changes were found when age was controlled in statistical analyses (repeated measures Mancova) (Table 3). No effect on cognition was traced on a patient during the follow-up whether he was on cART for at least 10 years continuously, for less than 10 years, had an interruption of cART , or low nadir CD4.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 3. Cognitive functioning of the 17 HIV infected patients at 3 follow-up examinations.

Year of examination **Follow-up time/years**	**1986-90** **0**	**1997** **7-11**	**2013** **23-27**	**Manova/Anova****		**Effect size**
	mean (sd)*	mean (sd)	Mean (sd)	F	p value	Eta Square
Cognitive function						
Memory				1.920	0.172	0.390
WMS Logical memory	11.9 (2.1)	13.8 (2.5)	10.0 (2.6)	-	-	-
List learning	57.9 (6.2)	61.9 (5.4)	57.3 (7.4)	-	-	-
Reasoning				0.895	0.496	0.230
WAIS Similarities	21.9 (1.7)	21.3 (1.8)	20.9 (2.0)	-	-	-
WAIS Block Design	40.9 (6.5)	41.5 (5.3)	37.9 (6.1)	-	-	-
Executive function				0.330	0.953	0.099
Trail-Making B	85.3 (21.5)	99.4 (29.8)	105.9 (27.2)	-	-	-
Stroop Interference test (time)	104.2 (24.8)	99.2 (22.6)	115.5 (34.8)	-	-	-
Speed of performance				1.221	0.353	0.289
WAIS Digit Symbol	59.3 (11.0)	55.4 (16.8)	48.9 (12.7)	-	-	-
Stroop Naming (time)	55.4 (11.6)	57.0 (11.4)	67.4 (15.7)	-	-	-

* raw scores
** age is used as a covariate

The neuroradiological follow-up showed only a minimal age-related increase in atrophic changes. The mean bicaudate ratio was 0,12 in 1997 and 0,13 in 2013, and the mean width of the third ventricle was 0,57 cm and 0,68 cm respectively. Two of the patients showed a slightly more prominent increase in atrophy. Four patients had new WMHIs. Three of the patients had new lacunar infarcts, one of which was already seen in 1997. One of the three patients had as well microhemorrhages not seen in 1997. One of these stroke patients was the eldest (75-year-old) of our study group and had some decline in his neuropsychological performance. However, the other patients with mild brain atrophy or stroke seen in the MRI had no detectable decline in cognitive performance.

A CSF sample was taken in 2013 was from 9 subjects. HIV-1 in CSF was below 20 copies/ml in eight subjects. The amplification test failed technically from one sample. About half of the subjects

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

had elevated protein or immunoglobulin in CSF (Table 4). The leucocyte count and immunoglobulin-albumin ratio were within the normal range in most subjects studied (Table 4).

Table 4. Cerebrospinal fluid of 9 subjects in 2013

	Median	**Range**	**Over upper limit of normal**
Protein, mg/l	451	268 – 675	5 / 9
Leucocytes	1	0 - 4	1 / 9
Immunoglobulin	31	10 - 82	4 / 9
Ig index	0.60	0.55 – 0.70	4 / 9
Ig / Alb index	0.16	0.09 – 0.22	1 / 9

Five patients had positive HBcAb indicating an earlier hepatitis B infection. None of them, however, were HBsAg positive, so none of the patients were chronically infected with hepatitis B. One patient had a positive syphilis serology with history, and a serological follow-up of an adequate treatment of syphilis. All patients were HCVAb negative.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

DISCUSSION

This study shows for the first time that HIV-1 infected patients who receive adequate anti-HIV therapy may preserve their neurological and neurocognitive function well despite of a history of HIV infection up to 30 years.

All cART-medication regimes are reducing the risk of the severest forms of HAND. Nevertheless, milder forms have been reported becoming more common,[25,26]. HIV is transported from the periphery through the BBB in the CNS with both monocytes and CD4 cells,[27,28]. In the CNS the monocytes transfer HIV into macrophages and microglial cells, both of which can produce HIV virions. HIV infection may either be hematogenous, "autonomous" when viral replication takes place in the CNS or a mixture of both,[27]. Astrocytes also become infected with HIV, but HIV does not replicate in astrocytes. The infected macrophages and microglial cells elicit an inflammatory reaction, which leads to recruitment of more infected immune cells in the brain,[28]. Further astrocytes contribute to the damage of brain by producing neurotoxic factors, like glutamate,[26]. The only known therapy reducing the CNS damage by HIV is ART. Even a monotherapy with zidovudine decreases the amount of inflammatory reaction in the cerebrospinal fluid (CSF),[29]. The modern cART regimens inhibit the replication of HIV almost completely in the periphery. These regimens have been shown to reduce the HIV viral load to an undetectable level in the CNS in most patients,[30]. The inflammation markers in the CSF may persist at an elevated level even after four years of virologically successful cART,[31]. Our results indicate that cognitive function can be preserved in HIV infected patients for a couple of decades despite the probable inflammatory activity in the CNS.

It is described that some HIV infected patients have a viral escape of HIV in the CNS in spite of a successful cART in the periphery,[32]. The phenomenon is fairly rare, affecting a minority of patients receiving a successful cART. Taking into account of the laboratory investigations, clinical

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

examinations and brain MRI made, it appears our cohort did not include such persons. The factors contributing to the good cognitive state in our patients probably include a long-term ART which on the average had been 19 years, of which on the average 13 years had been on cART. Secondly, the lack of drug abuse which is perhaps synergistic with HIV to cause HAND. The CHARTER study recruited 1555 HIV infected subjects across the USA and found that 52 % of them had at least mild neuropsychological impairment,[2]. In this study sample about a third (28 %) were using some recreational drugs. Thirdly, the good neurocognitive outcome is caused most likely by biological variation in our patients' properties to resist HIV infection, and their willingness to start ART. Fourth, lack of hepatitis C infection may contribute to the good neurocognitive outcome of our patients,[33, 34].

The only significant neurological impairment detected in our study population was peripheral neuropathy. Apart from one patient with extrapyramidal signs, no signs of other central nervous system impairment were found in clinical examination. The earlier ART has probably contributed to the development of neuropathy, because many patients had used deoxynucleoside analogues, which are known to cause toxic neuropathy, as a part of their ART.

A great proportion of our patients had diseases that constitute risks for cerebrovascular diseases. However, the only risk factor that was significantly higher than in the general population of Finland, was expectedly the prevalence of hypercholesterolemia. This is a well-known side effect of cART, especially the group of protease inhibitors,[35, 36]. Diabetes, hypertension and hypercholesterolemia were treated appropriately, which also decreased the risks for neurological and neurocognitive defects.

Although the neuropsychological raw scores declined especially between the second and last examination, no significant differences were found when the effect of age was controlled. Thus, the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

decline may be explained by the normal aging effects as the follow-up period was almost 30 years, the patients being in the average of 57 years at the time of the last examination.

In the MRI the signs of silent strokes support the research, which shows an increase of the incidence of stroke in the aging HIV-population,[37,38]. Only two of our patients had developed brain tissue atrophy that was more significant than in generally healthy aging men (annually 0.1-0.3 %),[39,40].

The limitations of the study include the survival benefit and small sample size. It may well be that our population of survivors from the era when anti-HIV medication was not available or did not give a long-term suppression of HIV-1 replication represent a subgroup of HIV infected persons who tolerate the infection better than men in the average. On the other hand, the recruited study group represents almost a half of the HIV infected persons treated in Aurora Hospital during the 1980s.

In conclusion our results give credence to the view that HIV-1 infected persons may preserve well their neurocognitive function when cART is started in time and delivered well, and when other conditions that may threaten the brain are treated appropriately. Apart from polyneuropathy, no significant neurological or neuropsychological trend of impairment were found in our study group. It is possible that the prevalence of neurocognitive impairment in the CHARTER study may not apply to all HIV-1 infected populations.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ACKNOWLEDGEMENTS

The authors thank Outi Debnam, RN, for practical assistance in conducting this study.

COMPETING INTERESTS

Terttu Heikinheimo: travel expenses from AbbVie, Bayer and Orion.

Erja Poutiainen: travel expenses and consultations from AbbVie.

Oili Salonen: no interests.

Irina Elovaara: no interests.

Matti Ristola: Honoraria, consultations, or travel expenses from Abbvie, BMS, Gilead, GSK, Janssen, and Merck. Grants for scientific activities from AbbVie and GSK.

FUNDING STATEMENT

This work was supported by an unrestricted research grant for the intervention in 2013 through the Clinical Research Institute of HUCH by AbbVie. Terttu Heikinheimo received support from Helsinki University Hospital research funds, Maire Taponen foundation and Orion research funds.

CONTRIBUTORSHIP STATEMENT

All authors included on the paper fulfil the four criteria of authorship according to ICMJE recommendation, TH is the corresponding author. In addition EP and IE collected the original data and the evaluations during 1986-1990 and year 1997. EP and TH produced the statistical data, OS analysed the MRI images from 1997 and 2013. MR evaluated the HIV infection in 1997 and 2013, and organised the evaluation of the cohort in 2013. EP did the neuropsychological assessment and TH the neurological assessment.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

[1] Monforte A, Cinque P, Mocroft A, *et al*. Changing Incidence of Central Nervous System Diseases in the EuroSIDA Cohort. *Annals of Neurology* 2004;**55**:320-328.

[2] Heaton RK, Clifford DB, Franklin DR,Jr, *et al*. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 2010;**75**(23). doi:10.1212/WNL.0b013e318200d727; 10.1212/WNL.0b013e318200d727.

[3] Heaton RK, Franklin DR, Ellis RJ, *et al*. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 2011;**17**(1). doi:10.1007/s13365-010-0006-1; 10.1007/s13365-010-0006-1.

[4] Simioni S, Cavassini M, Annoni JM, *et al*. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010;**24**(9). doi:10.1097/QAD.0b013e3283354a7b; 10.1097/QAD.0b013e3283354a7b.

[5] Ances BM, Clifford DB. HIV-associated neurocognitive disorders and the impact of combination antiretroviral therapies. *Curr Neurol Neurosci Rep* 2008;**8**(6).

[6] Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. *Nat Rev Immunol* 2005;**5**(1). doi:10.1038/nri1527.

[7] Sattentau QJ. Cell-to-Cell Spread of Retroviruses. *Viruses* 2010;**2**(6). doi:10.3390/v2061306 [doi].

[8] Eriksson S, Graf EH, Dahl V, *et al*. Comparative analysis of measures of viral reservoirs in HIV-1 eradication studies. *PLoS Pathog* 2013;**9**(2). doi:10.1371/journal.ppat.1003174 [doi].

[9] Pierson T, McArthur J, Siliciano RF. Reservoirs for HIV-1: mechanisms for viral persistence in the presence of antiviral immune responses and antiretroviral therapy. *Annu Rev Immunol* 2000;**18**. doi:18/1/665 [pii].

[10] Kivela PS, Krol A, Salminen MO, *et al*. Determinants of late HIV diagnosis among different transmission groups in Finland from 1985 to 2005. *HIV Med* 2010;**11**(6). doi:10.1111/j.1468-1293.2009.00783.x; 10.1111/j.1468-1293.2009.00783.x.

[11] Poutiainen E, Elovaara I, Raininko R, *et al*. Cognitive decline in patients with symptomatic HIV-1 infection. No decline in asymptomatic infection. *Acta Neurol Scand* 1996;**93**(6).

[12] Poutiainen E, Elovaara I, Salonen O, *et al*. Cognitive performance and brain atrophy in the long term follow-up of HIV-1-infected patients [abstract]. *22nd International Neuropsychological Society Mid-Year Conference* 1999.

[13] Poutiainen E. Cognitive deficits and emotional disorders in HIV-1 infected individuals. *Acta Psychiatr Scand* 1995;**92**(6).

[14] Poutiainen E, Elovaara I, Raininko R, *et al*. Cognitive performance in HIV-1 infection: relationship to severity of disease and brain atrophy. *Acta Neurol Scand* 1993;**87**(2).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

[15] Poutiainen E, Elovaara I. Subjective complaints of cognitive symptoms are related to psychometric findings of memory deficits in patients with HIV-1 infection. *J Int Neuropsychol Soc* 1996;**2**(3).

[16] Krupp LB, LaRocca NG, Muir-Nash J*, et al*. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;**46**(10).

[17] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**(11).

[18] Wechsler D. *Manual for the Wechsler Memory Scale-Revised.*. San Antonio, Texas: The Psychological Corporation 1987.

[19] Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th Ed. New York: Oxford University Press, 2004.

[20] Wechsler D. Wechsler adult intelligence scale. Manual. New York: The Psychological Corporation, 1955.

[21] Army Individual Test Battery. Manual of directions and scoring. 1944;.

[22] Stroop JR. Studies in interference in serial verbal reactions. *Journal of Experimental Psychology* 1935; **18**, 643-662.

[23] Beck AT, Beck RW. Screening depressed patients in family practice. A rapid technic. *Postgrad Med* 1972;**52**(6).

[24] Fazekas F, Chawluk JB, Alavi A*, et al*. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987;**149**(2). doi:10.2214/ajr.149.2.351 [doi].

[25] Chan P, Brew BJ. HIV Associated Neurocognitive Disorders in the Modern Antiviral Treatment Era: Prevalence, Characteristics, Biomarkers, and Effects of Treatment. *Curr HIV/AIDS Rep* 2014;. doi:10.1007/s11904-014-0221-0 [doi].

[26] Brew BJ, Chan P. Update on HIV Dementia and HIV-Associated Neurocognitive Disorders. *Curr Neurol Neurosci Rep* 2014;**14**(8). doi:10.1007/s11910-014-0468-2 [doi].

[27] Spudich SS, Nilsson AC, Lollo ND*, et al*. Cerebrospinal fluid HIV infection and pleocytosis: relation to systemic infection and antiretroviral treatment. *BMC Infect Dis* 2005;**5**. doi:1471-2334-5-98 [pii].

[28] Kraft-Terry SD, Stothert AR, Buch S*, et al*. HIV-1 neuroimmunity in the era of antiretroviral therapy. *Neurobiol Dis* 2010;**37**(3). doi:10.1016/j.nbd.2009.12.015 [doi].

[29] Elovaara I, Poutiainen E, Lahdevirta J*, et al*. Zidovudine reduces intrathecal immunoactivation in patients with early human immunodeficiency virus type 1 infection. *Arch Neurol* 1994;**51**(9).

[30] Robertson KR, Robertson WT, Ford S*, et al*. Highly active antiretroviral therapy improves neurocognitive functioning. *J Acquir Immune Defic Syndr* 2004;**36**(1). doi:00126334-200405010-00003 [pii].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

[31] Yilmaz A, Price RW, Gisslen M. Antiretroviral drug treatment of CNS HIV-1 infection. *J Antimicrob Chemother* 2012;**67**(2). doi:10.1093/jac/dkr492 [doi].

[32] Eden A, Fuchs D, Hagberg L, *et al*. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis* 2010;**202**(12). doi:10.1086/657342 [doi].

[33] Vivithanaporn P, Nelles K, DeBlock L, *et al*. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *J Neurol Sci* 2012;**312**(1-2). doi:10.1016/j.jns.2011.08.025 [doi].

[34] Devlin KN, Gongvatana A, Clark US, *et al*. Neurocognitive effects of HIV, hepatitis C, and substance use history. *J Int Neuropsychol Soc* 2012;**18**(1). doi:10.1017/S1355617711001408 [doi].

[35] Penzak SR, Chuck SK. Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment. *Scand J Infect Dis* 2000;**32**(2).

[36] Muronya W, Sanga E, Talama G, *et al*. Cardiovascular risk factors in adult Malawians on long-term antiretroviral therapy. *Trans R Soc Trop Med Hyg* 2011;**105**(11). doi:10.1016/j.trstmh.2011.07.016; 10.1016/j.trstmh.2011.07.016.

[37] Benjamin LA, Bryer A, Emsley HC, *et al*. HIV infection and stroke: current perspectives and future directions. *Lancet Neurol* 2012;**11**(10). doi:10.1016/S1474-4422(12)70205-3; 10.1016/S1474-4422(12)70205-3.

[38] Chow FC, Regan S, Feske S, *et al*. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr* 2012;**60**(4) (accessed 20120709). doi: http://dx.doi.org/10.1097/QAI.0b013e31825c7f24.

[39] Xu J, Kobayashi S, Yamaguchi S, *et a*l. Gender effects on age-related changes in brain structure. *AJNR Am J Neuroradiol* 2000;**2**1(1).

[40] Ge Y, Grossman RI, Babb JS, *et a*l. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. *AJNR Am J Neuroradiol* 2002;**2**3(8).

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Research Checklist

THREE DECADE NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page	Item No	Recommendation
Title and abstract	2	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	2		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	4	2	Explain the scientific background and rationale for the investigation being reported
Objectives	4	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	5	4	Present key elements of study design early in the paper
Setting	5	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
	–		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	5-8	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	5-8	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	-	9	Describe any efforts to address potential sources of bias
Study size	5	10	Explain how the study size was arrived at

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Quantitative variables		11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	8	12	(*a*) Describe all statistical methods, including those used to control for confounding
			(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) If applicable, explain how loss to follow-up was addressed
			(*e*) Describe any sensitivity analyses
Results			
Participants	9	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	9		(b) Give reasons for non-participation at each stage
	-		(c) Consider use of a flow diagram
Descriptive data	9,10	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	10		(b) Indicate number of participants with missing data for each variable of interest
	12		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	-	15*	Report numbers of outcome events or summary measures over time
Main results	10-12	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
	-		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses		17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Key results	14	18	Summarise key results with reference to study objectives
Limitations	16	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	14-15	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	16	21	Discuss the generalisability (external validity) of the study results
Other information			
Funding	17	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

THREE DECADES NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY IN FINLAND

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-007986.R2
Article Type:	Research
Date Submitted by the Author:	19-Sep-2015
Complete List of Authors:	Heikinheimo, Terttu; Helsinki University Central Hospital, Neurology Poutiainen, Erja; University of Helsinki, Institute of Behavioral Sciences; Helsinki University Central Hospital, Salonen, Oili; Helsinki University Central Hospital, Department of Radiology Elovaara, Irina; University of Tampere, Neurology Ristola, Matti; Helsinki University Central Hospital, Infectious diseases
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Neurology, Infectious diseases
Keywords:	INFECTIOUS DISEASES, Dementia < NEUROLOGY, HIV & AIDS < INFECTIOUS DISEASES, Adult neurology < NEUROLOGY, Infectious disease/HIV < NEUROLOGY

SCHOLARONE™
Manuscripts

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

THREE DECADES NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY IN FINLAND

Heikinheimo T[1], Poutiainen E[1,2], Salonen O[3], Elovaara I[4], Ristola M[5]

Correspondence to: [1]Dr. Terttu Heikinheimo, Department of Neurology, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00290, Helsinki, Finland.

Tel: + 358 9 4717 2662, Fax: +358 9 4717 4056

E-mail: terttu.heikinheimo-connell@hus.fi

[2]Rehabilitation Foundation, Helsinki, Finland.

[3]Department of Radiology, Helsinki University Central Hospital, Helsinki, Finland.

[4]Neuroimmunology Unit, Medical School, University of Tampere, Tampere, Finland.

[5]Department of Infectious Diseases at Aurora Hospital, Helsinki University Central Hospital, Helsinki, Finland

Key words: HIV, cognitive impairment, neuroAIDS, HAND

Tables: 4

References: 40

Word count: Abstract 293, Article 3393 (not including tables).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ABSTRACT

Objectives: Is it possible to live without any neurocognitive or neurological symptoms, when being infected with HIV for a very long time? These study-patients with decades long HIV infection in Finland were observed in this follow-up study in three time periods: 1986-1990, in 1997 and in 2013.

Setting: The patients from greater Helsinki area were selected from outpatients' unit of infectious diseases.

Participants: The study included 80 HIV-patients. Patients with heavy alcohol consumption, central nervous system disorder or psychiatric disease were excluded.

Primary and secondary outcome measures: The patients underwent neurological and neuropsychological examinations, magnetic resonance imaging of the brain and laboratory tests including the blood CD4-cells, plasma HIV-1 RNA. Neuropsychological examination included several measures: subtests of Wechsler Adult Intelligence Scale, Wechsler Memory Scale-Revised, list learning, Stroop, and Trail-Making-B test. The Beck Depression Inventory, and Fatigue Severity Scale were done. The obtained data from the three time periods were compared with each other.

Results: Due to high mortality, of the original 80 patients, 17 participated in all three examinations performed 1986-2013. The time from the HIV-diagnosis was 27 (23 to 30) years. The blood CD4-cells at the diagnosis were 610 (29 to 870)cells/mm3, and the nadir CD4 168 (4 to 408)cells/mm3. The time on combined antiretroviral treatment was 13 (5 to 17) years.

Nine patients suffered from fatigue, five had polyneuropathy, and three had lacunar cerebral infarcts. There was a subtle increase of brain atrophy in two patients. Mild depressive symptoms were common. The neuropsychological follow-up showed typical age-related cognitive changes. No HIV-associated dementia features were detected.

Conclusions: Polyneuropathy, fatigue and mild depression were common but more severe neurological abnormalities were absent. These long-term surviving HIV-seropositive patients, while

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

on best-available treatment, showed no evidence of HIV-associated neurocognitive disorder in neuropsychological and neuroradiological evaluations.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ARTICLE SUMMARY: STRENGTHS OF THIS STUDY

- A very long term, meticulous follow-up of HIV infected patients.
- The study evaluated almost a half of the Finnish HIV population during 1986-1990.
- A systematic neuropsychological and neurological, neuroimaging and HIV infection assessment is included.

LIMITATIONS OF THIS STUDY

- A small study sample.
- Survival bias.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

INTRODUCTION

Human immunodeficiency virus (HIV) has been challenging the mankind for more than 30 years. The virus crosses the blood-brain barrier (BBB) and enters the central nervous system (CNS) at the early stage of the infection - and never leaves it again. Without treatment HIV gradually causes a variety of neurological complications including HIV-associated neurocognitive disorder (HAND). This can vary from clinically asymptomatic or mild neurocognitive disorder to, when severest, HIV associated dementia (HAD). With the development of combined antiretroviral therapy (cART) patients with good adherence can live a long symptom-free life, and HAD has become rare,[1]. cART does not eliminate the virus, however, and it is claimed that a substantial portion of patients still develop neurocognitive impairments,[2-5]. A low level of cell-to-cell viral replication occurs also during the most successful cART-regimens,[6,7]. Even during effective cART there is a latent reservoir of blood CD4-cells carrying the HIV-genome, which is competent for replication,[8,9]. Low nadir CD4 seems to predict at least partially reversible HAND,[2]. Very long-term follow-up studies about the evolution of neurocognitive function among HIV infected patients are lacking. To our knowledge this is the first study describing a group of patients followed up even to 30 years.

Public health care provides HIV treatment in Finland. In the Helsinki-area, the infectious disease unit at Aurora Hospital has provided medical treatment for HIV infection since 1983,[10]. The first antiretroviral agent, zidovudine, became available at Aurora Hospital in 1987. A cohort study was started 1986 lasting five years to examine the CNS-symptoms associated with HIV infection,[11]. The HIV infected subjects were then reinvestigated in 1997,[12]. For this study we re-invited the subjects in 2013 with the purpose of obtaining a longitudinal evaluation of neurocognition, and the neurological and neuroimaging findings of a group of persons who became infected with HIV-1 more than 25 years ago, and who have been treated with optimal therapy. In Finland antiviral HIV-medication is free for patients through the Finnish communicable disease legislation.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

METHODS

Centre and patients

This is an observational follow-up study of HIV infected patients who were first enrolled in the neurological and neuropsychological examination during the years 1986-1990,[13,14]. HIV infection and AIDS are reportable diseases in Finland. The first patient with an HIV infection was diagnosed in 1983,[10]. The infectious disease unit at Aurora Hospital in Helsinki takes care of HIV infected individuals within the greater Helsinki area. The hospital managed a total of 98 HIV infected patients in 1986. The number of patients increased every year to 248 by the year 1991. Around half of these patients (n=106) were for the first time evaluated for this study during the years of 1986-1990. The exclusion criteria were: history of CNS-disease or present HIV-related CNS-disease (not HAD), severe dementia, marked learning disability, prominent alcohol consumption (scale 4, see below) and refusal of participation. Thus, 85 patients participated in the initial study,[13, 15]. Later, the subjects with previously diagnosed psychiatric problems; a further 5 patients were excluded. Thus the study cohort available for the follow-up totalled 80 persons. We have included in this analysis those patients who were re-invited and agreed to participate in all three study interventions in 1986-1990,[11], 1997,[12], and 2013.

Study interventions

During all three examination periods the detailed medical history was taken together with information on their educational background, profession and occupation. From each patient's medical records and previous research records, the following data were recorded: dates of acquisition and diagnosis of HIV infection, the history of the antiretroviral therapy, and the start of cART and possible interruptions of the therapy. Virologically suppressive therapy was defined as having most plasma HIV viral loads below the limit of detection before the year 2000 and below 50 copies/mL thereafter. Blood CD4-cells (cells/mm^3) within the year from diagnosis and nadir CD4

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(The lowest blood CD4-cells value measured since patient's HIV diagnosis), the date of plasma HIV-1 RNA level being below 400 copies and below 50 copies, and any AIDS events were recorded. Patients were further divided into two groups depending on whether they had used cART for more than 10 years continuously versus patients with less than 10 years of cART, or treatment interruptions. In another dividing patients with low nadir CD4 (<200 cells/mm^3) to higher nadir CD4 values were compared.

The diagnosis of other conditions were recorded from the medical records, and using information from the patient: medication or diet used for diabetes mellitus, hypertension (treated, or a history of hypertension as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both), hypercholesterolemia (treated or total cholesterol level ≥5.0 mmol/L, low-density lipoprotein level ≥3.0 mmol/L, or high-density lipoprotein level <1.0 mmol/L), and cardiovascular disease (prior diagnosis of coronary heart disease or myocardial infarction (MI)). Diagnosis of nephropathy or signs of protein in urine were recorded. Any history of depression or bipolar disorder, diagnosis of epilepsy or dementia was asked. Patients were also questioned about their smoking habits, and whether they used any illegitimate drugs. Alcohol consumption was estimated (scale 0-4) in the first and last evaluations,[15]. In the scale, 0 means infrequent use (0-100g alcohol per week), 1 = social drinker (101-250 g), 2 = moderate user (251-350 g), 3 = heavy drinker (351-500 g), and 4 meaning alcohol abuser (>500 g). The body mass index was calculated for all patients to estimate their nutritional status (underweight BMI ≤ 18.5 kg/m²) and obesity (BMI ≥30 kg/m²).

Neurological Investigations.

In 2013, all the subjects completed a fatigue severity scale (FSS) form translated in to Finnish to determine the level of fatigue patients were experiencing,[16]. The FSS has nine statements with a score range of 1-7. The patient accords a value based on how well the statement reflects his

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

condition during the previous week. A total score ≥ 36 (max 63) in the FSS suggests the patient is suffering from fatigue,[16].

In the year 2013 assessment, the diagnosis of polyneuropathy or treatment of neuropathic pain were recorded.

Each subject underwent a neurological evaluation performed by a neurologist in all three time periods. In 2013, we used a neurostatus scoring system and the Expanded Disability Scale Status (EDSS),[17]. The neurostatus is divided in to the domains of visual, brainstem, pyramidal, cerebellar, sensory and bowel/bladder. We excluded the cerebral domain, because we undertook neuropsychological investigations with more detailed information. Each domain gives the patient a functional system score (FS) where 0-1 means no symptoms, signs only; 2-3 = mild symptoms and signs; 3 = moderate symptoms and signs; 4-6 = severe symptoms and signs. The domains are used to determine patients EDSS together with patient's ability to walk (ambulatory). Both the neurostatus and EDSS are used widely to estimate the functional disability of patients with multiple sclerosis. For this study they were adapted with the purpose to standardizing the neurological status and making the clinical neurological examination easier to analyse quantitatively.

Neuropsychological investigation

The neuropsychological examination included measures of memory: the Logical Memory I of the Wechsler Memory Scale –Revised (WMS-R),[18], and a list learning task,[19]. The reasoning was assessed using Similarities and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS),[20]. The executive functions were assessed with the Trail Making B,[21] and the Interference subtask of the Stroop colour word test,[22]. The speed of performance was measured with the Digit Symbol subtest of the WAIS and a naming subtest of the Stroop colour word test. Depression was evaluated with a short form of the Beck Depression Inventory (BDI),[23]. All subjects were investigated with the same neuropsychological tests in all three study periods

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Neuroradiological investigation

MRI was performed on 16 patients both in years 1997 and 2013. The first brain MRI was performed using the 1.5 T unit (Siemens, Vision). The MRI protocol included conventional T2, FLAIR, T2 coronal and T1 MPR sagittal images. The second imaging in the year 2013 was performed using the 3 T unit (Philips, Achieva). The MRI protocol included as well the T2*, SWI and DWI axial sequences.

All brain abnormalities including infarcts and bleedings were recorded. The white matter hyperintensities (WMHIs) were classified as periventricular WMHIs or deep WMHIs, and graded 0 through 3. The severity of white matter lesions (WMLs) was rated with the Fazekas scale,[24]. The bicaudate ratios and the width on the third ventricle were measured to estimate the brain atrophy.

Laboratory investigations

Apart from the HIV laboratory workout mentioned above, the following laboratory assessment was made: a complete blood count, liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total bilirubin), kidney function (creatinine, protein in urine), plasma glucose and lipids (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL] and triglycerides), viral hepatitis serology (hepatitis B antigens [HBsAg, HBcAb], hepatitis C antigen [HCVAb], syphilis serology (treponema pallidum haemagglutination [TPHA] and cardiolipin antigens [VDRL]).

A current cerebrospinal fluid (CSF) sample was available of nine subjects for routine analysis.

Statistics

Statistical analyses were computed using IBM statistics software SPSS v.22.00. The neuropsychological parameters were analysed with multivariate analyses of variance (Manovas)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

controlling the effect of age in all analyses. In the analysis of other parameters simple parametric and nonparametric tests, and simple descriptive statistics were used as appropriate.

Ethics

This research was approved by the medical ethical committee of the Hospital District of Helsinki and Uusimaa. All patients gave their written informed consent to participate in the study.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

RESULTS

After exclusions the original study group consisted of 80 patients during the period 1986-1990. By 1997 evaluation, 47 patients had passed away, 7 had been lost for the follow-up, and 3 patients refused the follow-up evaluation, and consequently 23 patients were evaluated in 1997. Between 1997 and the current evaluation a further five patients had passed away, two of them because of AIDS-related deaths after 1997, and three of them because of non-AIDS related causes four or more years after 1997. For the latest evaluation, we were able to contact 18 HIV infected patients to participate in the neurological, neuropsychological, radiological and laboratory work-up. The patients were all men. They had a sexually acquired HIV infection, 16 through homo or bisexual contact and two through a heterosexual contact. All 18 patients gave their consent to participate in the study. One of them was too ill to participate in extended investigations and was only visited by the neurologists. His EDSS was 9.0. During the intervention in 2013 he died. No signs of HIV-associated brain damage were observed in post mortem autopsy. The results of the remaining 17 patients are reported here.

The demographic and clinical characteristics are presented in table 1. Out of the 17 patients, 11 (65 %) had had low nadir CD4 of < 200 cells/mm^3, and three (18 %) had had AIDS events (one patient with oesophageal candida, one with Pneumocystis pneumonia, and one with Kaposi's sarcoma and Pneumocystis pneumonia. The patient with two AIDS illnesses had had convulsions twice while receiving treatment Pneumocystis pneumonia). There were no elite controllers of HIV-1 viraemia among the subjects, whose median of the maximal HIV-1 viral load in plasma was 145000 copies/ml (range 10900 to 9360000 copies/ml). The median year of starting the first antiretroviral therapy was 1992 (range 1989 to 2002). Nine patients had had continuously virologically suppressive antiretroviral therapy for 10 years or longer. The remaining eight patients had had interruptions of suppressive antiretroviral therapy or had had continuously suppressive antiretroviral therapy for less than 10 years. The current antiretroviral combinations are shown in Table 2.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 1: Demographic and clinical characteristics of the study population. The number of patients (n) is 17 unless mentioned otherwise.

Charasteristic (unit)	Median	Range
Age / years	57.0	46-75
Education/ years	12.0	9-23
HIV infection[a]/ years n=16	28	23-31
HIV-diagnosis[b]/ years	27	23-30
CD4 at diagnosis[c] / cells/mm^3 n=15	610	29-870
nadir CD4 / cells/mm3	168	4-408
ARV / years	19	9-24
cART / years	13	5-17
BMI / kg/m^2	23.4	17.5-34.3
EDSS	2.0	1.0-4.0
FSS	32	9-63

[a] = patients own estimation about time from HIV infection. [b] = time from the HIV-diagnosis. [c]= the first blood CD4 cells, within the year from the diagnosis. ARV = use of any antiretroviral therapy. cART = antiretroviral therapy consisting of at least 3 agents. BMI = body mass index, EDSS = Expanded disability status scale, FSS = Fatigue Status scale

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 2: Current cART-regimens of 17 HIV infected patients.

cART-regime	Number of patients	Remarks
2NRTI+boosted PI	7	
2NRTI+NNRTI	3	
2NRTI+INSTI	1	
1NRTI+boostedPI+INSTI	1	intolerance to NRTI's
1NRTI+boostedPI+NNRTI	1	1 class ART resistance
NNRTI+boostedPI+INSTI	2	2 class ART resistance in both patients
2NRTI+boostedPI+NNRTI+INSTI	2	3 class ART resistance in both patients

NNRTI= non-nucleoside reverse transcriptase inhibitor, 2NRTI = two nucleoside reverse transcriptase inhibitors, PI = protease inhibitor, INSTI = integrase strand transfer inhibitor

Depression was diagnosed and treated in four (24 %) patients. In the results of BDI, between the three study time periods no significant changes appeared: BDI mean scores were 4.65, 5.53 and 5.00, respectively (Friedman, Chi ^{2} = 0.5, p=0.779) indicating mild depressive symptoms. The BDI result did not vary between the groups of low nadir CD4 or patients with cART therapy for more than 10 years. Hypertension was medicated and treated in five (29 %) men. Diabetes was diagnosed in two subjects. Nephropathy was diagnosed in two patients; one caused by diabetes and the other by prostatic hyperplasia, while two other subjects had protein in urine. Dyslipidemia was diagnosed in 11 (65%) of the patients. One patient was underweight (BMI 17.5 kg/m^2) and one obese (BMI 34.3 kg/m^2). Alcohol consumption has been moderate and was reduced significantly between the first and last examination (mean score±SD: 0.82±.0.64 vs. 0.35 ± 0.79, Wilcoxon, Z = -2.3, p = 0.021).

Tobacco smoking was a habit of 7 (41 %) patients. One patient informed that he occasionally used marihuana. None of the subjects used iv-drugs or other illegitimate drugs.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Four of the patients had a diagnosis of neuropathy. On clinical neurological examination an additional patient had signs of neuropathy (Sensory FS 3.0-4.0). Four of 5 patients with neuropathy had been treated with deoxynucleosides, 4 with stavudine from 3 to 10 years, and 3 with didanosine from 3 to 4.5 years. Only one patient with neuropathy had not been treated with deoxynucleosides. Altogether 6 patients had EDSS between 3.0 and 4.0 (mean = 3.4) indicating moderate disability. In five of them this was due to neuropathy. One patient had mild extrapyramidal findings and bladder dysfunction that increased his EDSS. None of the patients had prominent loss of vision, cerebellar ataxia, marked pyramidal symptoms or other clear signs of central nervous system abnormalities. They were all fully ambulatory. Most of the patients (16) had intact sensation of smell.

The neuropsychological examination showed a mild decline in raw scores particularly between the second and last examination, but no significant changes were found when age was controlled in statistical analyses (repeated measures Mancova) (Table 3). No effect on cognition was traced on a patient during the follow-up whether he was on cART for at least 10 years continuously, for less than 10 years, had an interruption of cART , or low nadir CD4.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 3. Cognitive functioning of the 17 HIV infected patients at 3 follow-up examinations.

Year of examination	**1986-90**	**1997**	**2013**	**Manova/Anova****		**Effect size**
Follow-up time/years	**0**	**7-11**	**23-27**			
	mean (sd)*	mean (sd)	Mean (sd)	F	p value	Eta Square
Cognitive function						
Memory				1.920	0.172	0.390
WMS Logical memory	11.9 (2.1)	13.8 (2.5)	10.0 (2.6)	-	-	-
List learning	57.9 (6.2)	61.9 (5.4)	57.3 (7.4)	-	-	-
Reasoning				0.895	0.496	0.230
WAIS Similarities	21.9 (1.7)	21.3 (1.8)	20.9 (2.0)	-	-	-
WAIS Block Design	40.9 (6.5)	41.5 (5.3)	37.9 (6.1)	-	-	-
Executive function				0.330	0.953	0.099
Trail-Making B	85.3 (21.5)	99.4 (29.8)	105.9 (27.2)	-	-	-
Stroop Interference test (time)	104.2 (24.8)	99.2 (22.6)	115.5 (34.8)	-	-	-
Speed of performance				1.221	0.353	0.289
WAIS Digit Symbol	59.3 (11.0)	55.4 (16.8)	48.9 (12.7)	-	-	-
Stroop Naming (time)	55.4 (11.6)	57.0 (11.4)	67.4 (15.7)	-	-	-

* raw scores
** age is used as a covariate

The neuroradiological follow-up showed only a minimal age-related increase in atrophic changes. The mean bicaudate ratio was 0,12 in 1997 and 0,13 in 2013, and the mean width of the third ventricle was 0,57 cm and 0,68 cm respectively. Two of the patients showed a slightly more prominent increase in atrophy. Four patients had new WMHIs. Three of the patients had new lacunar infarcts, one of which was already seen in 1997. One of the three patients had as well microhemorrhages not seen in 1997. One of these stroke patients was the eldest (75-year-old) of our study group and had some decline in his neuropsychological performance. However, the other patients with mild brain atrophy or stroke seen in the MRI had no detectable decline in cognitive performance.

A CSF sample was taken in 2013 was from 9 subjects. HIV-1 in CSF was below 20 copies/ml in eight subjects. The amplification test failed technically from one sample. About half of the subjects had elevated protein or immunoglobulin in CSF (Table 4). The leucocyte count and immunoglobulin-albumin ratio were within the normal range in most subjects studied (Table 4).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Table 4. Cerebrospinal fluid of 9 subjects in 2013

	Median	**Range**	**Over upper limit of normal**
Protein, mg/l	451	268 – 675	5 / 9
Leucocytes	1	0 - 4	1 / 9
Immunoglobulin	31	10 - 82	4 / 9
Ig index	0.60	0.55 – 0.70	4 / 9
Ig / Alb index	0.16	0.09 – 0.22	1 / 9

Five patients had positive HBcAb indicating an earlier hepatitis B infection. None of them, however, were HBsAg positive, so none of the patients were chronically infected with hepatitis B. One patient had a positive syphilis serology with history, and a serological follow-up of an adequate treatment of syphilis. All patients were HCVAb negative.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

DISCUSSION

This study shows for the first time that Finnish HIV-1 infected patients who receive adequate anti-HIV therapy may preserve their neurological and neurocognitive function well despite of a history of HIV infection up to 30 years.

All cART-medication regimes are reducing the risk of the severest forms of HAND. Nevertheless, milder forms have been reported becoming more common,[25,26]. HIV is transported from the periphery through the BBB in the CNS with both monocytes and CD4 cells,[27,28]. In the CNS the monocytes transfer HIV into macrophages and microglial cells, both of which can produce HIV virions. HIV infection may either be hematogenous, "autonomous" when viral replication takes place in the CNS or a mixture of both,[27]. Astrocytes also become infected with HIV, but HIV does not replicate in astrocytes. The infected macrophages and microglial cells elicit an inflammatory reaction, which leads to recruitment of more infected immune cells in the brain,[28]. Further astrocytes contribute to the damage of brain by producing neurotoxic factors, like glutamate,[26]. The only known therapy reducing the CNS damage by HIV is ART. Even a monotherapy with zidovudine decreases the amount of inflammatory reaction in the cerebrospinal fluid (CSF),[29]. The modern cART regimens inhibit the replication of HIV almost completely in the periphery. These regimens have been shown to reduce the HIV viral load to an undetectable level in the CNS in most patients,[30]. The inflammation markers in the CSF may persist at an elevated level even after four years of virologically successful cART,[31]. Our results indicate that cognitive function can be preserved in HIV infected patients for a couple of decades despite the probable inflammatory activity in the CNS.

It is described that some HIV infected patients have a viral escape of HIV in the CNS in spite of a successful cART in the periphery,[32]. The phenomenon is fairly rare, affecting a minority of patients receiving a successful cART. Taking into account of the laboratory investigations, clinical

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

examinations and brain MRI made, it appears our cohort did not include such persons. The factors contributing to the good cognitive state in our patients probably include a long-term ART which on the average had been 19 years, of which on the average 13 years had been on cART. Secondly, the lack of drug abuse which is perhaps synergistic with HIV to cause HAND. The CHARTER study recruited 1555 HIV infected subjects across the USA and found that 52 % of them had at least mild neuropsychological impairment,[2]. In this study sample about a third (28 %) were using some recreational drugs. Thirdly, the good neurocognitive outcome is caused most likely by biological variation in our patients' properties to resist HIV infection, and their willingness to start ART. Fourth, lack of hepatitis C infection may contribute to the good neurocognitive outcome of our patients,[33, 34].

The only significant neurological impairment detected in our study population was peripheral neuropathy. Apart from one patient with extrapyramidal signs, no signs of other central nervous system impairment were found in clinical examination. The earlier ART has probably contributed to the development of neuropathy, because many patients had used deoxynucleoside analogues, which are known to cause toxic neuropathy, as a part of their ART.

A great proportion of our patients had diseases that constitute risks for cerebrovascular diseases. However, the only risk factor that was significantly higher than in the general population of Finland, was expectedly the prevalence of hypercholesterolemia. This is a well-known side effect of cART, especially the group of protease inhibitors,[35, 36]. Diabetes, hypertension and hypercholesterolemia were treated appropriately, which also decreased the risks for neurological and neurocognitive defects.

Although the neuropsychological raw scores declined especially between the second and last examination, no significant differences were found when the effect of age was controlled. Thus, the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

decline may be explained by the normal aging effects as the follow-up period was almost 30 years, the patients being in the average of 57 years at the time of the last examination.

In the MRI the signs of silent strokes support the research, which shows an increase of the incidence of stroke in the aging HIV-population,[37,38]. Only two of our patients had developed brain tissue atrophy that was more significant than in generally healthy aging men (annually 0.1-0.3 %),[39,40].

The limitations of the study include the survival benefit and small sample size. It may well be that our population of survivors from the era when anti-HIV medication was not available or did not give a long-term suppression of HIV-1 replication represent a subgroup of HIV infected persons who tolerate the infection better than men in the average. On the other hand, the recruited study group represents almost a half of the HIV infected persons treated in Aurora Hospital during the 1980s.

In conclusion our results give credence to the view that HIV-1 infected persons may preserve well their neurocognitive function when cART is started in time and delivered well, and when other conditions that may threaten the brain are treated appropriately. Apart from polyneuropathy, no significant neurological or neuropsychological trend of impairment were found in our study group. It is possible that the prevalence of neurocognitive impairment in the CHARTER study may not apply to all HIV-1 infected populations.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

ACKNOWLEDGEMENTS

The authors thank Ms.Outi Debnam, RN, for practical assistance in conducting this study. We also thank Tim Connell for proofreading the article.

COMPETING INTERESTS

Terttu Heikinheimo: travel expenses from AbbVie, Bayer and Orion.

Erja Poutiainen: travel expenses and consultations from AbbVie.

Oili Salonen: no interests.

Irina Elovaara: no interests.

Matti Ristola: Honoraria, consultations, or travel expenses from Abbvie, BMS, Gilead, GSK, Janssen, and Merck. Grants for scientific activities from AbbVie and GSK.

FUNDING STATEMENT

This work was supported by an unrestricted research grant for the intervention in 2013 through the Clinical Research Institute of HUCH by AbbVie. Terttu Heikinheimo received support from Helsinki University Hospital research funds, Maire Taponen foundation and Orion research funds.

CONTRIBUTORSHIP STATEMENT

All authors included on the paper fulfil the four criteria of authorship according to ICMJE recommendation: designing the study, analysing and interpreting of data for the work, revising the work critically and approving of the version to be published. All authors are accountable for all the aspects of the work. TH is the corresponding author and drafted the first versions of the article. EP and IE collected the original data and the evaluations during 1986-1990 and year 1997. EP and TH

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

produced the statistical data, OS analysed the MRI images from 1997 and 2013. MR evaluated the HIV infection in 1997 and 2013, and organised the evaluation of the cohort in 2013. EP did the neuropsychological assessment and TH the neurological assessment.

DATA SHARING

Extra data is available by emailing: Terttu.heikinheimo-connell@hus.fi

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

REFERENCES

[1] Monforte A, Cinque P, Mocroft A, *et al*. Changing Incidence of Central Nervous System Diseases in the EuroSIDA Cohort. *Annals of Neurology* 2004;**55**:320-328.

[2] Heaton RK, Clifford DB, Franklin DR,Jr, *et al*. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 2010;**75**(23). doi:10.1212/WNL.0b013e318200d727; 10.1212/WNL.0b013e318200d727.

[3] Heaton RK, Franklin DR, Ellis RJ, *et al*. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 2011;**17**(1). doi:10.1007/s13365-010-0006-1; 10.1007/s13365-010-0006-1.

[4] Simioni S, Cavassini M, Annoni JM, *et al*. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010;**24**(9). doi:10.1097/QAD.0b013e3283354a7b; 10.1097/QAD.0b013e3283354a7b.

[5] Ances BM, Clifford DB. HIV-associated neurocognitive disorders and the impact of combination antiretroviral therapies. *Curr Neurol Neurosci Rep* 2008;**8**(6).

[6] Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. *Nat Rev Immunol* 2005;**5**(1). doi:10.1038/nri1527.

[7] Sattentau QJ. Cell-to-Cell Spread of Retroviruses. *Viruses* 2010;**2**(6). doi:10.3390/v2061306 [doi].

[8] Eriksson S, Graf EH, Dahl V, *et al*. Comparative analysis of measures of viral reservoirs in HIV-1 eradication studies. *PLoS Pathog* 2013;**9**(2). doi:10.1371/journal.ppat.1003174 [doi].

[9] Pierson T, McArthur J, Siliciano RF. Reservoirs for HIV-1: mechanisms for viral persistence in the presence of antiviral immune responses and antiretroviral therapy. *Annu Rev Immunol* 2000;**18**. doi:18/1/665 [pii].

[10] Kivela PS, Krol A, Salminen MO, *et al*. Determinants of late HIV diagnosis among different transmission groups in Finland from 1985 to 2005. *HIV Med* 2010;**11**(6). doi:10.1111/j.1468-1293.2009.00783.x; 10.1111/j.1468-1293.2009.00783.x.

[11] Poutiainen E, Elovaara I, Raininko R, *et al*. Cognitive decline in patients with symptomatic HIV-1 infection. No decline in asymptomatic infection. *Acta Neurol Scand* 1996;**93**(6).

[12] Poutiainen E, Elovaara I, Salonen O, *et al*. Cognitive performance and brain atrophy in the long term follow-up of HIV-1-infected patients [abstract]. *22nd International Neuropsychological Society Mid-Year Conference* 1999.

[13] Poutiainen E. Cognitive deficits and emotional disorders in HIV-1 infected individuals. *Acta Psychiatr Scand* 1995;**92**(6).

[14] Poutiainen E, Elovaara I, Raininko R, *et al*. Cognitive performance in HIV-1 infection: relationship to severity of disease and brain atrophy. *Acta Neurol Scand* 1993;**87**(2).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

[15] Poutiainen E, Elovaara I. Subjective complaints of cognitive symptoms are related to psychometric findings of memory deficits in patients with HIV-1 infection. *J Int Neuropsychol Soc* 1996;**2**(3).

[16] Krupp LB, LaRocca NG, Muir-Nash J*, et al*. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;**46**(10).

[17] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**(11).

[18] Wechsler D. *Manual for the Wechsler Memory Scale-Revised.*. San Antonio, Texas: The Psychological Corporation 1987.

[19] Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th Ed. New York: Oxford University Press, 2004.

[20] Wechsler D. Wechsler adult intelligence scale. Manual. New York: The Psychological Corporation, 1955.

[21] Army Individual Test Battery. Manual of directions and scoring. 1944;.

[22] Stroop JR. Studies in interference in serial verbal reactions. *Journal of Experimental Psychology* 1935; **18**, 643-662.

[23] Beck AT, Beck RW. Screening depressed patients in family practice. A rapid technic. *Postgrad Med* 1972;**52**(6).

[24] Fazekas F, Chawluk JB, Alavi A*, et al*. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987;**149**(2). doi:10.2214/ajr.149.2.351 [doi].

[25] Chan P, Brew BJ. HIV Associated Neurocognitive Disorders in the Modern Antiviral Treatment Era: Prevalence, Characteristics, Biomarkers, and Effects of Treatment. *Curr HIV/AIDS Rep* 2014;. doi:10.1007/s11904-014-0221-0 [doi].

[26] Brew BJ, Chan P. Update on HIV Dementia and HIV-Associated Neurocognitive Disorders. *Curr Neurol Neurosci Rep* 2014;**14**(8). doi:10.1007/s11910-014-0468-2 [doi].

[27] Spudich SS, Nilsson AC, Lollo ND*, et al*. Cerebrospinal fluid HIV infection and pleocytosis: relation to systemic infection and antiretroviral treatment. *BMC Infect Dis* 2005;**5**. doi:1471-2334-5-98 [pii].

[28] Kraft-Terry SD, Stothert AR, Buch S*, et al*. HIV-1 neuroimmunity in the era of antiretroviral therapy. *Neurobiol Dis* 2010;**37**(3). doi:10.1016/j.nbd.2009.12.015 [doi].

[29] Elovaara I, Poutiainen E, Lahdevirta J*, et al*. Zidovudine reduces intrathecal immunoactivation in patients with early human immunodeficiency virus type 1 infection. *Arch Neurol* 1994;**51**(9).

[30] Robertson KR, Robertson WT, Ford S*, et al*. Highly active antiretroviral therapy improves neurocognitive functioning. *J Acquir Immune Defic Syndr* 2004;**36**(1). doi:00126334-200405010-00003 [pii].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

[31] Yilmaz A, Price RW, Gisslen M. Antiretroviral drug treatment of CNS HIV-1 infection. *J Antimicrob Chemother* 2012;**67**(2). doi:10.1093/jac/dkr492 [doi].

[32] Eden A, Fuchs D, Hagberg L*, et al*. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis* 2010;**202**(12). doi:10.1086/657342 [doi].

[33] Vivithanaporn P, Nelles K, DeBlock L*, et al*. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *J Neurol Sci* 2012;**312**(1-2). doi:10.1016/j.jns.2011.08.025 [doi].

[34] Devlin KN, Gongvatana A, Clark US*, et al*. Neurocognitive effects of HIV, hepatitis C, and substance use history. *J Int Neuropsychol Soc* 2012;**18**(1). doi:10.1017/S1355617711001408 [doi].

[35] Penzak SR, Chuck SK. Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment. *Scand J Infect Dis* 2000;**32**(2).

[36] Muronya W, Sanga E, Talama G*, et al*. Cardiovascular risk factors in adult Malawians on long-term antiretroviral therapy. *Trans R Soc Trop Med Hyg* 2011;**105**(11). doi:10.1016/j.trstmh.2011.07.016; 10.1016/j.trstmh.2011.07.016.

[37] Benjamin LA, Bryer A, Emsley HC*, et al*. HIV infection and stroke: current perspectives and future directions. *Lancet Neurol* 2012;**11**(10). doi:10.1016/S1474-4422(12)70205-3; 10.1016/S1474-4422(12)70205-3.

[38] Chow FC, Regan S, Feske S*, et al*. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr* 2012;**60**(4) (accessed 20120709). doi: http://dx.doi.org/10.1097/QAI.0b013e31825c7f24.

[39] Xu J, Kobayashi S, Yamaguchi *S, et a*l. Gender effects on age-related changes in brain structure. *AJNR Am J Neuroradiol* 2000**;2**1(1).

[40] Ge Y, Grossman RI, Babb J*S, et a*l. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. *AJNR Am J Neuroradiol* 2002**;2**3(8).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Research Checklist

THREE DECADES NEUROLOGICAL AND NEUROCOGNITIVE FOLLOW-UP OF HIV-1 INFECTED PATIENTS ON BEST AVAILABLE ANTIRETROVIRAL THERAPY IN FINLAND

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page	Item No	Recommendation
Title and abstract	2	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	2		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	5	2	Explain the scientific background and rationale for the investigation being reported
Objectives	5	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	6	4	Present key elements of study design early in the paper
Setting	6	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
	–		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	6-9	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	7-9	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	-	9	Describe any efforts to address potential sources of bias
Study size	6	10	Explain how the study size was arrived at

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

Quantitative variables		11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9-10	12	(*a*) Describe all statistical methods, including those used to control for confounding
			(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) If applicable, explain how loss to follow-up was addressed
			(*e*) Describe any sensitivity analyses
Results			
Participants	11	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	11		(b) Give reasons for non-participation at each stage
	-		(c) Consider use of a flow diagram
Descriptive data	11-13	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	11		(b) Indicate number of participants with missing data for each variable of interest
	12		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	-	15*	Report numbers of outcome events or summary measures over time
Main results	13-16	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
	-		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses		17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only

Key results	17	18	Summarise key results with reference to study objectives
Limitations	19	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	18-19	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	19	21	Discuss the generalisability (external validity) of the study results
Other information			
Funding	20	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-007986 on 5 November 2015. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml