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DISSERTATION

SCREENING FOR HAND:

Validation of the International HIV Dementia Scale as a screening tool for HIV-Associated Neurocognitive Disorders in a German-speaking population

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“A la memòria i pel record d’aquells
que han patit el cruel oblit de la demència.”

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADC	AIDS Dementia Complex
ADL	Activities of Daily Living
AIDS	Acquired Immunodeficiency Syndrome
ANI	Asymptomatic Neurocognitive Impairment
AUC	Area Under the Curve
cART	Combined Antiretroviral Treatment
CASPe	Critical Appraisal Skills Programme
CNS	Central Nervous System
COWA	Controlled Oral Word Association Test
CPE	CNS Penetration-Effectiveness
CROI	Conference on Retroviruses and Opportunistic Infections
CSF	Cerebrospinal fluid
DNAA	Deutsche Neuro-AIDS Arbeitsgemeinschaft e.V.
DTI	Diffusion Tensor Imaging
fMRI	Functional Magnetic Resonance Imaging
HAART	Highly-active antiretroviral therapy
HAD	HIV-Associated Dementia
HAND	HIV-Associated Neurocognitive Disorder
HDS	HIV Dementia Scale
HIV	Human Immunodeficiency Virus
IHDS	International HIV Dementia Scale
IQR	Interquartile range
JC-virus	John Cunningham virus
LPS-UT3	Horn’s Performance Test System, Subtest 3
MCMD	Minor Cognitive Motor Disorder
µL	Microlitre
mL	Millilitre
MND	Mild Neurocognitive Disorder
MNGC	Multinucleated giant cell
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MSM	Men who have sex with men
NCI	Neurocognitive impairment
NCN	Neurocognitively normal
NFL	Light chain neurofilament
NPV	Negative Predictive Value
PPV	Positive Predictive Value
RAVLT	Rey Auditory Verbal Learning Test
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristic
ROCF	Rey-Osterrieth Complex Figure Test
RVDLT	Rey Visual Design Learning Test
SD	Standard Deviation

TIRM	Turbo Inversion Recovery Magnitude
TMT	Trail Making Test
UNAIDS	Joint United Nations Programme on HIV/AIDS
VLMT	Verbaler Lern- und Merkfähigkeitstest
WAIS-III	Wechsler Adult Intelligence Scale

ABSTRACT IN ENGLISH

Background: HIV-associated neurocognitive disorders (HAND) are widely present among people living with HIV. Especially its milder forms, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), remain highly prevalent worldwide. Diagnosing these conditions is subject to a time and resource consuming neuropsychological assessment. Selecting patients at a higher risk of cognitive impairment by using a simple but effective screening tool helps to organise access to further neuropsychological diagnosis. The International HIV Dementia Scale (IHDS) has until now been a well-established screening tool in African and American countries, however these populations' demographics differ significantly from ours, so using the same parameters could be ineffective.

Objectives: The aim of this study is to calculate the prevalence of this condition among people attending an HIV outpatient clinic in Berlin and to validate the clinical use of the International HIV Dementia Scale as a screening tool for HAND on a German-speaking population.

Methods: For these purposes, we screened 480 HIV-infected patients using the IHDS, 89% of them were on a stable antiretroviral treatment. Ninety of them completed a standardised neuropsychological battery of tests and a specific cognitive complaints questionnaire. The same procedure was applied to a control group of 30 HIV-negative participants. HAND diagnosis was established according to the Frascati criteria. Sensitivity and specificity of the different IHDS cut-off values were also assessed.

Results: The overall prevalence of HAND in our cohort was 43% (20% ANI, 17% MND and 6% HIV-associated dementia). The optimal cut-off on the IHDS for detecting HAND cases was set at 11 and achieved both a sensitivity and a specificity of 80%. When specifically screening for the more severe form of HAND, HIV-associated dementia, a cut-off value of 10 offered an increase in both sensitivity (94%) and specificity (86%). The Youden Index for diagnostic accuracy was 0.6 and 0.8, respectively.

Conclusion: The prevalence of HAND is high despite the optimal proportion of participants on stable antiretroviral treatment and comparable to the reported by recent studies performed in countries with a similar economic development. Due to their predictive value, factors such as actively expressing cognitive complaints, a longer duration of the HIV infection and a lower $CD4^+$ nadir should be taken into account when designing future screening methods. The use of the IHDS proved to be easy, reliable and well integrated into the everyday routine of an HIV outpatient clinic. This study confirms the IHDS to be a useful HAND screening tool in primary care settings and establishes new recommendations for its use in German-speaking countries.

ZUSSAMMENFASSUNG AUF DEUTSCH

Hintergrund: HIV-assoziierte neurokognitive Defizite (HAND) bleiben weltweit hoch-prävalent. Dies betrifft vor allem die milderen Formen wie die asymptomatische neurokognitive Einschränkung (ANI) und das mildes neurokognitive Defizit (MND) Die Diagnose dieser Entitäten wird neben der Anamnese mit einer zeit- und ressourcenaufwändigen neuropsychologischen Untersuchung gestellt. Es erscheint daher sinnvoll, Risikopatienten durch ein geeignetes Screening zu detektieren, um den Zugang zur weiteren Diagnostik zu vereinfachen. Die *International HIV Dementia Scale* (IHDS) ist ein Screening-Instrument, das bisher in mehreren amerikanischen und afrikanischen Ländern validiert wurde. Da sich diese Patientenpopulationen in mehreren demographischen Faktoren von der hiesigen unterscheiden, erscheint die Verwendung des IHDS nicht gerechtfertigt.

Ziel: Ziel dieser Studie war die Validierung des IHDS als Screening-Test für HAND im deutschsprachigen Raum und die Berechnung der HAND-Prävalenz in einer Berliner HIV-Schwerpunktpraxis.

Methoden: 480 HIV-positive Patienten wurden mittels IHDS gescreent. 89% der Kohorte waren stabil auf eine kombinierte antiretrovirale Therapie (cART) eingestellt und stellten sich mehrheitlich quartalsmäßig zur Verlaufsbeurteilung in der Praxis vor. Neunzig Probanden unterzogen sich zusätzlich einer kompletten standardisierten neuropsychologischen Evaluierung und beantworteten einen spezifischen Fragebogen für die Erfassung subjektiver kognitiver Beschwerden. Das gleiche Verfahren wurde auf eine Kontrollgruppe von 30 HIV-negativen Teilnehmern angewendet. Die Diagnose HAND orientierte sich an den Frascati Kriterien. Die Sensitivität und Spezifität der verschiedenen Cut-off-Werte des IHDS wurden ebenfalls bewertet.

Ergebnisse: Die Prävalenz von HAND in unserer Kohorte lag bei 43% (20% ANI, 17% MND und 6% HIV-assoziierte Demenz). Mit einem Cut-off-Wert des IHDS von 11 konnte eine Sensitivität und Spezifität einschließlich der milderen Formen von HAND von 80% erreicht werden. Ein Cut-off-Wert von 10 erfasste hingegen vor allem schwerere Formen von HAND (HIV Demenz) (Sensitivität 94%, Spezifität 86%). Der Youden Index, ein Maß zur Beurteilung der Qualität eines diagnostischen Tests, lag bei 0,6 bzw. 0,8.

Schlussfolgerungen: Trotz der optimalen medizinischen Versorgung mit einem hohen Anteil an antiretroviral behandelten Patienten, ist die HAND Prävalenz in unserer Kohorte hoch. Sie ist jedoch vergleichbar mit Studienpopulationen in Ländern, welche eine ähnliche wirtschaftliche Entwicklung aufweisen. Faktoren wie die aktive Äußerung von kognitiven Beschwerden, eine längere Dauer der HIV-Infektion und ein niedriger $CD4^+$- Nadir sollten aufgrund des hohen prädiktiven Wert für HAND als unabhängige Faktoren in Betracht gezogen werden. Die Anwendung des IHDS zeigte sich als einfach, zuverlässig und gut in den regulären Alltag einer HIV Schwerpunktpraxis integrierbar. Diese Studie bestätigt damit die Nutzbarkeit des IHDS im allgemeinmedizinischen Bereich und validiert erstmals einen Cut-off für den deutschsprachigen Raum.

CHAPTER ONE: INTRODUCTION

1.1 HIV and the brain

The human immunodeficiency virus (HIV) is a slowly replicating retrovirus with well known neurotropism for perivascular macrophages, microglial cells and astrocytes. It is a is highly neurovirulent virus, producing both peripheral and central nervous pathology [1].

Neurological symptoms are reported to be the first manifestation of an HIV infection in approximately 10% of newly diagnosed people. During the course of their illness up to 60% of patients will suffer from a clinically evident neurological dysfunction. Several post mortem studies show that over 75% of people with advanced acquired immunodeficiency syndrome (AIDS) have evidence of degeneration in brain tissue, even without having shown any prior clinical symptoms [2-5].

HIV-associated central nervous system (CNS) pathology may be triggered by the direct action of the virus itself. This is known as primary aetiology, and includes diseases such as peripheral polyneuropathy and HIV-associated neurocognitive disorders (HAND). CNS-pathology may also be a consequence of the acquired immunological deficiency state, known as secondary aetiology. It includes autoimmune and neoplastic processes, such as CNS lymphoma and Kaposi sarcoma, as well as all opportunistic infections and their related diseases: toxoplasmosis, cytomegalovirus encephalitis, bacterial, viral and cryptococcal meningitis and the John Cunningham virus (JC-virus) induced progressive multifocal leukoencephalopathy.

Before the introduction of the highly-active antiretroviral therapy (HAART) in 1996 and even now in regions of the world where access to these drugs is limited, secondary causes and other comorbidities such as CNS tuberculosis are the main, immediate causes of death amongst patients with HIV-related neurological disease. In contrast, in countries where antiretroviral therapy is widely available, opportunistic infections tend to be less common − even rare − in well-treated immunocompetent patients. This has transformed HIV into a chronic infection and presented a further burden of neurological dysfunctions with more complex symptoms and a slower progression, such as peripheral polyneuropathy and HIV-associated neurocognitive disorders. Different studies have found that the prevalence of cognitive dysfunction in HIV-positive patients varies between 20% and 50% despite

effective antiretroviral therapy [6, 7], meaning that about half of the people living with HIV worldwide -between 25 and 35 million in 2012 according to UNAIDS data [8]- are at risk of developing some degree of associated cognitive disorder, including HIV dementia.

1.2 The neuropathology of HIV

The central nervous system works as an isolated compartment in the human body as it is functionally separated from the rest of it by the blood-brain barrier. This is a microvascular endothelial cell layer with selective permeability that enables the homeostasis of the cerebrospinal fluid (CSF) to be maintained. In an attempt to explain how the HIV virus accesses the CNS, several neuroinfection pathways have been proposed. The most commonly accepted theory is that the virus enters the CNS from the peripheral blood system as a passenger inside previously infected $CD4^+$ T cells and monocytes [9]. Alternatively, some models suggest that the virus accesses the CNS by direct transcytosis in tiny vesicles through the endothelial cell cytoplasm as well as by direct infection, but these two last events are thought to happen far less often than the previously described pathway [10].

Once inside the central compartment, these activated monocytes differentiate into perivascular macrophages. It is inside these macrophages where the virus starts its replication process, giving origin to the primary infection of the CNS. This is also supported by the existence of specific viral populations that differ from the ones in peripheral blood.

From the five CNS cell types that can potentially be infected – perivascular macrophages, microglial cells, astrocytes, oligodendrocytes and neurones – only the first two are capable of inducing HIV proliferation. This is due to the fact that both of these cells have a common embryological origin and express the $CD4^+$ and CCR5/CXCR4 receptors, used by the virus to access the cell, on their external membrane. The viral RNA is then built in the genome of the host cell and leads to the expression of viral-envelope glycoproteins at the membrane surface, which are antigenic. These interact with the gp41 receptors displayed on nearby non-infected macrophages and microglia, producing conglomerates of infected and uninfected cells known as multinucleated giant cells (MNGCs). These represent the pathological hallmark of HIV encephalitis.

Astrocytes may also be partially infected by the virus, but this infection is not considered to be fully productive. Nevertheless, a limited, partial expression of HIV genes in astrocytes may lead to the cell's dysfunction. Moreover, activated astrocytes will modify the normal functioning of the blood-brain barrier, leading to changes in the CSF homeostasis that could cause damage to brain tissue. Other viral proteins may also contribute to neurodegeneration: Gp120, Tat and Vpr are well known to be toxic to neurones and astrocytes. Finally, astrocytes replace the spaces left by dead cells after a process of long-lasting tissue damage. In the brains of untreated HIV-infected patients, this results in a strong proliferation of astrocytes.

Chemokines may also play an important role in the balance between neuronal deterioration and neuroprotection. All CNS cells have different kinds of chemokine receptors and are therefore affected by its release. However, the most important interaction between HIV and chemokines occurs in macrophages and microglia. The production of pro-inflammatory cytokines in perivascular macrophages seems to be increased when infected by the virus, causing vascular and tissue injury. Furthermore, these biomarkers increase the migration of infected, activated monocytes, and produce neurotoxins like quinolinic and archidonic acid, nitric oxide, PAF and TNF, which potentiate degeneration. Additionally, chemokines promote the activation and proliferation of microglia, astrocytes, and more macrophages. This leads to a vicious cycle of inflammation and degeneration of tissue.

Oligodendrocytes are responsible for producing the myelin sheath that protects the neuronal axons and contributes to a better conduction of the nervous impulse. This cell type remains largely uninfected, but is widely affected by indirect neurotoxicity as a consequence of the infection of other cell types. For example, viral envelope glycoprotein gp120 reduces the production of myelin and increases the concentration of intracellular calcium to apoptotic levels.

Neurones are the main effectors of cognitive and motor function. When their normal functioning is altered, people start experiencing limitations in memory, speech and motor skills, as well as in other higher functions. These represent the primary symptomatology observed in people affected by HAND and will be described in greater detail in the upcoming chapters. The neuronal degeneration cannot be explained as a direct effect of the virus, because this cell type does not express the $CD4^+$ receptor and remains therefore

uninfected. The damage is mainly due to a "bystander" effect, in which the general state of inflammation existing in the HIV-infected brain damages the neurones. These cells are affected by: the molecules liberated by activated perivascular macrophages, the dysregulation of homeostasis conducted by altered astrocytes, the positive and negative effects of several chemokines, and the Ca^{2+}-mediated gp120-induced apoptosis. All the previous events contribute to a general neuronal dysfunction and death of the surrounding cells.

1.3 The evolution of HAND

The first time AIDS and dementia were linked in a systematic way was in 1986, when R. W. Price grouped a set of symptoms he had observed in his AIDS patients, and named this condition AIDS Dementia Complex (ADC) [11]. Characterised by intellectual and cognitive impairment, personality and behavioural disturbances and motor dysfunctions such as ataxia, coordination and speech inability, its presentation was reminiscent of subcortical dementia. The ADC was a severe condition that initially caused short-term memory loss, mental slowing, reading and comprehension difficulties and apathy. Gait was also affected, with patients usually complaining of stumbling and tripping, accompanied by a postural tremor, which affected fine manual dexterity. It progressed rapidly from psychomotor slowing to dementia, followed by an akinetic mute state in which the patient became immobile and incapable of speaking, and finally to coma and death [12]. Without any treatment available, the mean survival of the diagnosed cases was around six months [13].

Then, in 1991, the American Academy of Neurology defined two levels of neurological manifestations of HIV infection in the brain, dividing Price's ADC into two entities: HIV-associated dementia (HAD) and minor cognitive motor disorder (MCMD) as well as publishing a structured diagnosis algorithm for both conditions [14]. Later, and after the vast changes that the implementation of HAART had represented, a need for adaptation emerged. Whereas the widespread use of combined antiretroviral therapies (cART) led to a marked decrease in the incidence of HIV-associated dementia by 15% to 50%, its prevalence experienced a rise due to the increased survival of those who were taking advantage of the therapy. HAART also introduced another change in the presentation of HIV-associated dementia: its severity got milder. The cognitive phenotypes were more mixed and included both cortical and subcortical features. The progression patterns

changed from being acute and progressive to chronic and of lower activity. In some cases, the impairment was reversible after starting antiretroviral treatment. Even so, in some subjects the progression continued unaltered even under correct systemic viral suppression, probably due to CNS virological escape. [6, 13, 15-17]. All these new observations were included in the last review of the definition, which was published in 2007. This update divided the condition into three entities and aggregated them under the generic term of HIV-associated neurocognitive disorders, or HAND. Commonly known as the "Frascati criteria", these latest diagnostic standards [18] are based on the following three conditions:

1. The performance of a neuropsychological battery of tests that assesses at least five different domains of cognition –including: verbal and language skills; attention and working memory; abstraction and executive function; memory including learning and recall; speed of information processing; motor skills; sensory-perceptual abilities-, each of them ideally being evaluated with at least two different tests.
2. The presence or absence of a limitation in activities of daily living (ADL).
3. No evidence of delirium, other dementias, depression, substance abuse or any other pre-existing or coexisting cause at the time of performing the neuropsychological evaluation.

Depending on the performance on the different neuropsychological tests and the grade of limitation in ADL, the HAND diagnosis is divided into three levels of severity:

Asymptomatic Neurocognitive Impairment (ANI)

Defines an acquired cognitive impairment in ≥2 ability domains, with ≥1.0 standard deviation (SD) below the mean for age-education-appropriate norms on standardised neuropsychological tests, in which at least one of the affected areas is cognitive. The cognitive impairment should not cause ADL impairment.

Mild Neurocognitive Disorder (MND)

Defines an acquired cognitive impairment in ≥2 ability domains, with ≥1.0 standard deviation (SD) below the mean for age-education-appropriate norms on standardised neuropsychological tests, in which at least one of the affected areas is cognitive. The cognitive impairment causes at least mild interference in everyday functioning: self-

reported reduced mental acuity, inefficiency at work, and problems in other social functions.

HIV-Associated Dementia (HAD)

Defines an acquired cognitive impairment in ≥2 ability domains, with ≥2.0 standard deviations (SD) below the mean for age-education-appropriate norms on standardised neuropsychological tests, in which at least one of the affected areas is cognitive. The cognitive impairment causes marked interference in everyday functioning: assistance is needed for medication intake, financial operations, shopping, preparing meals, housekeeping, maintaining schedules, understanding news, maintaining a job or taking care of children.

A simplified overview of this classification can be seen in Fig. 1.1.

	Pre-existing neurological or psychiatric condition	Cognitive impairment in ≥2 ability domains	Limitation in everyday living activities
ANI: Asymptomatic Neurocognitive Impairment	✗	✔ ≥1.0 SD	✗
MND: Mild Neurocognitive Disorder	✗	✔ ≥1.0 SD	✔
HAD: HIV-Associated Dementia	✗	✔ ≥2.0 SD	✔✔✔

Fig 1.1: Classification and diagnostic criteria of the different HAND entities

1.4 Diagnosing HAND

The HAND diagnosis starts with a complete neuropsychiatric examination. This is the main diagnostic step, and should be carried out for all HIV-infected patients experiencing concentration problems, memory loss, or any other neurological symptom. Several screening tools are available, and they might be used to assist diagnosis at this point. If results are outside the normal range, the patient should undergo a battery of neuropsychological tests in order to assess cognition.

An analysis of the CSF − obtained by lumbar puncture − should also be performed. This procedure provides a wealth of useful information. First of all, it allows us to obtain basic but valuable information of the CSF composition such as the actual concentrations of glucose, proteins and cellularity. Moreover, it allows us to measure the actual viral load in the central compartment, and compare it with the systemic viral load, revealing possible divergences between these two body compartments. A genotyping analysis can also highlight a possible divergence in the viral genetic populations between CSF and peripheral blood. This genetic test might be interesting to perform in cases of CNS viral escape [19]. In CSF we can also evaluate neuroinflammation markers, such as neopterine produced by activated perivascular macrophages, and ongoing neurodegeneration by determining the concentrations of the structural protein light chain neurofilament (NFL) [20]. Finally, the concentration of the different antiretroviral substances can also be measured.

A wide range of imaging techniques allow us to make a morphological approach to the HIV infected brain. These techniques go from simple projection radiology to more elaborate images obtained by complex techniques of morphometry such as diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), resting state fMRI and magnetic resonance spectroscopy [21-25].

Magnetic resonance imaging (MRI) is used routinely as the standard imaging technique in HAND diagnosis. Typical observations in the T2 turbo inversion recovery magnitude (TIRM) weighting include periventricular leukoencephalopathy and atrophy, especially in cases of advanced dementia. In cases of mild neurocognitive impairment, the MRI may not vary much from the one of a healthy, HIV-negative brain. Besides that, there is no direct correlation between the MRI findings and the cognitive impairment presented by the patient.

DTI is a functional MRI technique that allows the representation of the integrity of the white matter before the development of gliosis. Linda Chang presented a study in 2008 based on a cohort of 39 HIV-positive and 32 seronegative participants with follow-up over one year. The HIV-positive participants were divided between treatment naïve and treatment experienced − those who had been receiving cART for at least six months. The use of DTI showed a clear increase of the mean diffusivity in the frontal and parietal white

matter and its extension in the genu of the corpus callosum. In this case, the findings did correlate with the neuropsychological deficits [26]. Furthermore, in a subgroup analysis of a small cohort of 10 treatment experienced patients, the DTI parameters regarding neuroinflammation showed a marked improvement [27].

1.5 Differential diagnosis

Making a HAND diagnosis can be tricky, as patients with HIV infection frequently have complex medical and social backgrounds that may influence the psychometric results. Determining whether a neurocognitive impairment is due only to the HIV infection or to other pre-existing or co-occurring conditions is difficult. Every case should be considered individually, paying special attention to some major confounders and comorbidities, and conducting a careful differential diagnosis.

The most common confounder is depression [28, 29]. Low mood can occur as a symptom of HIV dementia itself, but also as an independent condition that does not necessarily reflect HAND. Alcohol and substance abuse can also be misleading, as it produces a decline in cognitive functioning, making it sometimes impossible to determine if the impairment is due to the effect of the substance, the viral infection or a combination of both. In these cases, the diagnosis of HAND should be deferred to a subsequent examination conducted at least one month after the end of the substance abuse or at a time when the major depression has submitted.

A cognitive decline can also be found in many non-HIV-related neurological conditions, such as mental development disabilities or traumatic brain injury. All these conditions should be ruled out before considering a HAND diagnosis.

In a context of an aging HIV population, a correct differential diagnosis should consider other types of dementia. Alzheimer's disease (AD) is the most common cause of dementia in Europe. It affects around 2% of the population over 65 years of age, and its incidence doubles with every increase of five years of age. Unlike HAND, Alzheimer’s exclusively affects cortical functions. Its emergence is insidious and its progression is slow, initially affecting recent memory and the ability to learn anything new. It progressively affects other higher functions such as language, visual recognition, visual-constructive abilities and task planning. Typical histological findings are intracellular deposits of tau protein and

beta amyloid plaques. These two changes help when diagnosing AD but are not pathognomonic, as they can also be found in a smaller proportion of individuals with other forms of dementia and in normal brains of elderly patients.

Vascular dementias are the second most common type. They occur as a result of multiple areas of cerebral infarction. The involvement can be cortical or subcortical, depending on the region affected by the stroke. This type of dementia is characterised by an abrupt onset and a fluctuating clinical course. Finally, it is important to point out that dementias can coexist: a combination of different dementias at different stage of progression can further complicate the HAND diagnostic scenario.

1.6 Comorbidities and related risk factors

Many studies have tried to reveal which factors may predict the onset and development of HAND. Demographic factors which have been associated with an increased incidence of the disease include advanced age [30], lower level of education [31], lower income and limited access to antiretrovirals [29]. Other factors directly related to the HIV infection such as a lower $CD4^+$ nadir [32], lower $CD4^+$ cell counts [28], very high systemic or CSF viral loads [29] and the time elapsed since the primary infection occurred [33] also demonstrated a negative influence in the neuropsychological outcome. The existence of specific viral clades with higher neurovirulence has also been postulated as a risk factor, although the latter has not yet been fully proven [34]. Furthermore, factors related to taking antiretrovirals such as low adherence, pauses in therapy and inability to achieve viral suppression [35] might widely contribute to neurological impairment, as well as the neurotoxicity associated with some substances, especially efavirenz [36]. Additionally, the CNS penetration index of the different components that form the antiviral regimen, known as CNS Penetration-Effectiveness Score, or CPE-Score, [29, 37] should also be considered. Finally, several studies reveal correlations between developing HAND and other comorbidities such as viral infections like hepatitis C [31, 38] and general cardiovascular risk factors like a higher Body-Mass-Index, the lack of physical activity, arterial hypertension, dyslipidaemia, diabetes mellitus and smoking [39].

1.7 Screening for HAND

The gold standard for diagnosing cognitive impairment is a complete neuropsychological assessment following the Frascati criteria. However, this is extremely time and resource

consuming and needs to be performed by a trained neuropsychologist, making it relatively unfeasible to implement and not compatible with the daily functioning of a standard outpatient HIV clinic. Therefore, there is an existing need for valid diagnostic screening tests.

In 1994 Power et al. [40] described a rapid screening test known as the HIV Dementia Scale (HDS) designed to identify patients with HIV Dementia. The HDS evaluates memory, attention, psychomotor speed and constructional abilities. It requires trained personnel in neurology as it includes an anti-saccadic eye movement evaluation. It takes about 10 minutes to administer and the maximum score is 16 points. A score of ≤10 suggests HAD.

Since then, several other screening tools have been proposed, all aiming to achieve levels of sensitivity and specificity as close as possible to the gold standard. They have had differing degrees of success, acceptance and popularity.

The International HIV Dementia Scale (IHDS), presented by Sacktor et al. [41] in 2005, was designed to be cross-cultural. It is easy to administer, takes less than five minutes, and unlike the HDS, it does not require a professional neurologist. It evaluates memory, motor speed and psychomotor speed. After publishing, it rapidly won popularity and was recommended in the European AIDS Clinical Society's guidelines in 2009. A 2013 systematic review of different HIV Dementia Scales calculated an estimated diagnostic accuracy based on 10 studies where the IHDS was used. It reported a pooled sensitivity of 74% and calculated a specificity of 55%. In the case of the HDS, the pooled sensitivity based on 13 studies was 68% and the specificity was 78%. The study concluded that both scales had low accuracy, and that the IHDS seemed less specific than the HDS [42].

More recently, the Montreal Cognitive Assessment (MoCA) has gained prominence for detecting HIV-associated neurocognitive impairment, although it still needs adaptation to HIV-specificities before it can be applied in most populations. Designed as a rapid screening instrument for mild cognitive dysfunction, it assesses different domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. It takes approximately 10 minutes to administer. The total possible score is 30 points, with the cut-off set at 26. The MoCA

includes several tests likely to be sensitive for HAND, including those for attention, concentration, working memory, executive functioning and reasoning [43]. A study presented at the 2011 Conference on Retroviruses and Opportunistic Infections (CROI) reported a sensitivity of 59% and a specificity of 81%. Sensitivity improved to 83% with a cut-off point of 28, but specificity reduced [44]. Finally, there is a wide range of computer-based test batteries available, but they all have limitations in testing verbal learning and are usually expensive [45, 46]. Table 1.1 shows the sensitivity and specificity of the discussed screening tools calculated by several research groups.

Table 1.1: Studies evaluating sensitivity and specificity of selected available screening tools

Screening Test	% Sensitivity	% Specificity	Referred literature
HDS	76	88	Power [40]
	75	60	Simioni [47]
	68	78	Haddow [42]
IHDS	80	55	Sacktor [41]
	70	65	Singh [48]
	55	82	Antinori [49]
	74	55	Haddow [42]
MoCA	59	81	Overton [44]

Some of these tools have achieved moderate to high levels of accuracy, especially when diagnosing HAD, but they still lack validity when it comes to diagnosing ANI and MND, the milder forms of HAND [28, 45]. To our knowledge, none of them have been validated for the use on patients in German-speaking countries, making us rely on the results of international studies with foreign populations, which might be similar to but not the same as ours.

1.8 Goals and hypotheses

The aims of this study are:

Firstly, to evaluate the practical use of the IHDS as a screening tool for detecting HAND in an HIV-positive, treatment-compliant population visiting a primary care and HIV-outpatient clinic in Berlin, Germany.

Secondly, to determine the capability of the IHDS to differentiate between HIV-positive patients with impaired neurocognitive function and HIV-positive patients with normal neurocognitive function.

Thirdly, to determine which cut-off value of the IHDS has the highest sensitivity, specificity and diagnostic accuracy for detecting HAND in the mentioned population.

Fourthly, with regard to the latter, to develop a new screening algorithm with recommendations on the use of the IHDS in German-speaking populations.

Fifthly, to evaluate the prevalence of HAND and its subtypes ANI, MND and HAD in the mentioned population.

Sixthly, to determine which of the factors that have been previously associated with developing HAND correlate better with the disease in the mentioned population.

The following hypotheses will be evaluated:

Hypothesis I: Cognition in HIV-positive participants is worse than in HIV-negative participants. This includes: I.1: HIV-positive participants report more neurocognitive complaints than HIV-negative controls. I.2: HIV-positive participants obtain lower scores in the neuropsychological evaluation than HIV-negative controls. I.3: The 'high performance' HIV-positive study group has a cognitive profile comparable to the HIV-negative control group.

Hypothesis II: The IHDS is a reliable screening tool for detecting HAND in primary care settings. The results obtained in the IHDS are consistent with the results of a complete neuropsychological evaluation.

Hypothesis III: When using the IHDS for screening for HAND, a cut-off value of 11 points is more useful than the official cut-off of 10 points.

Hypothesis IV: Several factors previously related with a higher risk for HAND, such as advanced patient age, longer duration of the HIV-infection, lower $CD4^+$ nadir, low $CD4^+$

cell count, hepatitis C coinfection or the neurotoxicity of several antiretrovirals like efavirenz are expected to correlate with a lower performance in the neurocognitive evaluation.

Hypothesis V: The prevalence of HAND and its subtypes in our cohort is comparable to the observed prevalence in cohorts from more economically developed countries.

CHAPTER TWO: METHODS

2.1 Participants

2.1.1 Inclusion and exclusion criteria

All participants in this study were between the ages of 19 and 80 years old, had a diagnosis of HIV-infection for at least three months, spoke fluent German and were healthy enough to attend the neuropsychological test. Participants were excluded if they had an acute opportunistic systemic or cerebral infection, cancer, had a history of opportunistic CNS infection or any other non-HIV related chronic-inflammatory CNS disease, had a current psychotic disorder or were currently using mind-altering substances of any kind.

2.1.2 Data protection and ethical issues

The ethics committee of the Charité School of Medicine in Berlin approved this study. The general terms of data protection and the Charité good medical and scientific practice statutes apply. All the study procedures were conducted in accordance with the 1964 Declaration of Helsinki (fourth revision).

All participants who met study eligibility were given detailed information about the study and provided with a written informed consent form. Only after signing this form were they finally recruited.

2.2 Screening process

Following the recommendations of the European AIDS Clinical Society [50], HIV-positive patients attending a Berlin primary care and infectious diseases clinic were screened for HAND. The screening was completed as part of the regular medical check-ups for all immunologically stable, healthy patients with no acute illness. The author performed all screening tests.

2.2.1 International HIV-Dementia Scale

The IHDS was designed to be a brief, easy to administer, cross-cultural screening tool to identify individuals at risk for HIV dementia in both the industrial and developing world [41]. This test consists of three parts. Each one of them analyses a specific cognitive domain and is scored with a maximum of four points, the final score being the sum of the three sub-scores and having a range from 0 to 12 points.

The first subtest is a simple finger-tapping test that assesses the patient's motor speed condition. The second subtest evaluates psychomotor speed and consists of a fist-palm-edge alternating hand position motor programming task. The third subtest is a memory test with immediate recall after two minutes of four words. In our case, we decided to modify the original words from the English version (dog, hat, bean, red) to more frequently used terms in German language: *Hund, Jacke, blau, Löffel* (dog, jacket, blue, spoon).

We decided to use this tool for our study because it is rapid to administer − less than five minutes − it is language and culturally neutral and can be performed by any physician without the need for specific neurological training. These three criteria are perfectly appropriate for the patients visiting the chosen primary care clinic, which has a high rate of international, urban clients.

2.2.2 Questionnaire of the DNAA - German NeuroAIDS Study Group

This questionnaire, attached as additional material on page 69, was designed by a group of leading German neurologists and psychiatrists working in the NeuroAIDS field to evaluate neurological abnormalities such as memory and motor impairment, depression and similar problems in HIV-positive patients.

Twenty-two yes/no questions have to be answered by the patient without help or interpretation from the administrator. Nine of these questions indicate mild interference in everyday functioning (ADL impairment), and therefore are useful for discerning between ANI and MND. The questionnaire also gives an idea of the patient's emotional status, being useful in identifying a current depressive episode.

2.2.3 Baseline interview

A general clinical history as well as infection and immunological data were collected after a short interview with every participant. This information was completed using the patients' electronic clinical history and introduced into an encrypted database. This data was used during the analysis phase to look for associations between potential risk factors for HAND and the score obtained in the IHDS.

Collected data included

• General information:	Age	(in years)
	Gender	(male / female)
• HIV-infection data:	Date of infection, if known	(MM/YYYY)
	Date first diagnosed	(MM/YYYY)
	Months since diagnosis	(in months)
	Current viral load	(cop/mL)
	Viral load zenith	(cop/mL)
	Current $CD4^+$ cell count	(cells/µL)
	$CD4^+$ nadir	(cells/µL)
• Therapy data:	Current cART combination	(substances)
	Months since cART-start	(in months)
	CPE 2010 Score	(1-99)
• Other information:	Neuropsychiatric events	(Yes/No)
	Diabetes mellitus	(Yes/No)
	Hepatitis C coinfection	(Yes/No)
	Hepatitis B coinfection	(Yes/No)
	Active syphilis	(Yes/No)
	Alcohol and substance use	(Yes/No)
• IHDS data:	Total score	(0-12)
	Motor speed subtest score	(1-4)

Psychomotor speed score	(1-4)
Memory-recall score	(1-4)

2.3 Sample for neuropsychological testing

2.3.1 Study groups

For the purpose of calculating the prevalence of HAND in our cohort, we designed three study groups.

The original sample of 480 participants who completed the IHDS was divided according to the IHDS score obtained into three subsamples: The 'poor performance' subsample (n = 49, 10%) included participants with a score of 10 points or fewer, the 'average performance' subsample (n = 87, 18%) scored between 10.5 and 11 points, and the 'high performance' subsample (n = 344, 72%) scored either 11.5 or 12 points.

Then, thirty members of each subsample were randomly selected to establish three study groups – with identical names as the subsamples – and to undergo neuropsychological examination.

2.3.2 Control group

We also recruited a control group from of HIV-negative participants from the same clinic. They had the same eligibility and exclusion criteria, except that this group had documentation of a negative HIV test one year prior to the evaluation, usually within the previous few weeks. This group also consisted of 30 participants and was matched with the 'high performance' study group for gender, age (±2 years), educational level (±2 years) and IHDS score.

2.3.3 Sample size calculation

The estimated sample size needed to undergo neuropsychological testing in order to calculate the condition's prevalence was set at 120, divided in four subgroups of 30 participants. This had a relative precision of ±7.8% at a confidence level of 95%.

Similarly, for the determination of the IHDS's sensitivity and specificity, this same sample of 120 participants had a relative precision of ± 12,5% at a confidence level of 95%. In this case, the global prevalence of HAND was assumed to be 50%, and the IHDS's sensitivity and specificity were estimated to be 0.80 and 0.57, respectively. These last values were based on the available literature and data published by Sacktor et al. [41] in prior studies.

These estimates were calculated using EpiDat 4.1, available on-line at dxsp.sergas.es.

2.4 Neuropsychological assessment

All participants were assessed by a battery of medical, neurological, psychiatric, social and demographic measures before performing the neuropsychological tests, in addition to the information already obtained in the screening's baseline interview. Results were individually evaluated and explained verbally and in writing to every participant after completion of the assessment.

2.4.1 Preliminary interview

If at the time of the neuropsychological evaluation the screening test was more than three months old, this test was repeated and the study group changed if necessary, in order to maintain the correct correlation with the assigned study group,. Further information was also collected on that day:

- Educational level (in years)
- Current occupation (described)
- Acute illness (Yes/No)
- Current awareness of neurocognitive limitations (Yes/No)
- Depressed mood (Yes/No)

2.4.2 Neuropsychological battery of tests

For the purpose of this study study we put together a neuropsychological testing battery with 11 different tests covering eight ability domains. The average time to completion of

the tests was about 150 minutes per participant. The author performed all evaluations after completing training in neuropsychology. Table 2.1 shows each test with its evaluated domain(s) and its literature references. A wider description of each test follows.

Table 2.1: Tests contained in neuropsychological battery			
Test name	Evaluated neurocognitive areas or domains according to the Frascati definition	Reference	Explanation on page
Rey Auditory Verbal Learning Test (RAVLT)	Domain 4: Learning and recall – memory (verbal)	[51, 52][ae]	21
Rey Visual Design Learning Test (RVDLT)	Domain 4: Learning and recall - memory (figural)	[53, 54][a]	21
Rey-Osterrieth Complex Figure Test (ROCF)	Domain 6: Sensory-perceptual abilities Domain 4: (Visual) memory	[55-57][a]	22
Digit Span	Domain 2: Attention / working memory Domain 4: (Short-term) memory	[58] [ae]	22
Horn's Performance Test System, Subtest 3 (LPS-UT3)	Domain 8: Logical thinking / Non-verbal intelligence level*	[59] [ae]	23
d2 Test of Attention – Revised Version	Domain 2: Attention / working memory	[60] [ae]	23
Colour-Word-Interference Test	Domain 3: Executive function / abstraction	[61] [ae]	24
Controlled Oral Word Association Test (COWA), Subtests S-Words and Subtest Animals [62]	Domain 1: Language/verbal fluency	[62] [ae]	25
Trail Making Test (TMT), Part A	Domain 5: Speed of information processing	[63-65] [ae]	25
Trail Making Test (TMT), Part B	Domain 2: Attention / working memory Domain 3: Executive function / abstraction		
Wechsler Adult Intelligence Scale (WAIS-III), Subtest Digit Symbol-Coding	Domain 5: Speed of information processing	[66] [ae]	26
Grooved Pegboard	Domain 7: Motor skills	[67, 68] [aeg]	26

** This domain not included in the Frascati definition, but needed for evaluation of other tests.* a: adjusted for age; e: adjusted for educational level; g: adjusted for gender.

2.4.2. 1. Rey Auditory Verbal Learning Test (RAVLT)

⇒ *Tests Domain 4: Learning and recall – memory (verbal)*

This is an easy to administer, paper-based test with the purpose of assessing verbal learning, interference susceptibility and short-term, medium-term and recognition of words. We used the German version of the test by Helmstaedter [51, 52] known as *Verbaler Lern- und Merkfähigkeitstest (VLMT)*.

This consists of 15 unrelated nouns that are read aloud five times by the examiner. The order of the words remains the same each time. After each word spoken out loud the examinee has a short period of time to repeat the words he remembered. After the fifth repetition an interference list "B" of 15 new words is read and repeated by the patient. Immediately after that, the examinee is asked to recall the words from the first list, "A", without a prior reading of these words (immediate recall). Recall of this first list is also requested after a further 20-minute period of time (delayed recall). Finally, a printed sheet that includes both words from list "A" and "B" and another 20 extra nouns with phonetic or semantic similarities is shown and the patient is asked to identify only the words from list "A".

Scoring: A point is scored for each remembered word in each of the five initial attempts, with the maximum score for the first five attempts being 75 points. The score from the interference list, the immediate and delayed recall attempts and in the recognition exercise is also written down. Wrongly recognised words are also recorded.

2.4.2. 2. Rey Visual Design Learning Test (RVDLT)

⇒ *Tests Domain 4: Learning and recall - memory (figural)*

In a similar way to the RAVLT, this paper-based test evaluates figural learning, interference susceptibility and short-term and medium-term memory of geometric figures [53, 54].

Fifteen unrelated figures are shown to the patient. Each one is presented on an individual card and at a speed of one figure every two seconds. After showing the cards, the figures

are drawn by the examinee on a sheet of paper with 15 small boxes. This process is repeated five times. After a 20-min delay period, the examinee is required to identify the target figures in a matrix that includes the 15 previously shown and 15 similar but previously unseen figures.

Scoring: There is a point for each correctly drawn figure, with a maximum score of 75 points. Designs that are unclear or upside down are considered incorrect. The score obtained in the recognition trial is also recorded.

2.4.2. 3. Rey-Osterrieth Complex Figure Test (ROCF)

⇒ *Tests Domain 6: Sensory-perceptual abilities*

⇒ *Tests Domain 4: (Visual) memory*

The purpose of this test is to assess visual-spatial constructional ability and visual memory [55-57].

The examinee is asked to copy a given complex figure, thus testing his visual-spatial constructional ability. Immediately after copying and again after a 30 minute delay he is asked to reproduce the figure based on memory. For each drawn detail a score from zero to two is given depending on its presence, completeness and position in the overall picture. There are 18 details that are combined for a maximum score of 36 points.

2.4.2. 4. Digit Span

⇒ *Tests Domain 2: Attention / working memory*

⇒ *Tests Domain 4: (Short-term) memory*

This test has been designed to evaluate the examinees short-term and working memory. It is a subtest included in a wider memory testing kit known as the Wechsler Memory Scale. For the purposes of this study we used a revised version adjusted for a German speaking population [58].

To assess the short-term memory performance, the subject is asked to repeat strings of digits of increasing length in the same order (forwards) as recited by the examiner. To

capture the working memory performance the examinee then repeats them in the reverse order (backwards).

The forward version begins with a string of three numbers. The backward version starts with two numbers. At each level of difficulty two strings are read out loud. The examinee needs to fulfil at least one correct string at each level of difficulty in order to proceed to the next level with longer strings. If none of the number series are reproduced correctly, the test ends.

Scoring: For each correctly reproduced string a point is given, equalling 12 as the maximum score in each of the two sections of the test.

2.4.2. 5. Horn's Performance Test System, Subtest 3 (LPS-UT3)

⇒ *Tests Domain 8: Logical thinking / Non-verbal intelligence level*

The subtest 3 of the Performance Test System according to Horn [59] is a German-designed test to determine the ability of logical thinking and can be used to estimate the current levels of intelligence.

Although this domain is not described in the Frascati criteria needed to diagnose a HAND, it is needed for the normalisation of the results obtained in the subsequent Word-Colour-Stroop test.

The participant is given a sheet of paper with various figures that follow a logical principle pattern structure. In each exercise, there is a figure that does not follow the logical rule. This illogical figure has to be identified and crossed out by the examinee. The test consists of 40 exercises of increasing difficulty. The participant has five minutes to resolve the maximum possible number of rows of figures.

Scoring: A point is obtained for each correctly crossed out item, with 40 being the highest score possible.

2.4.2. 6. d2 Test of Attention – Revised Version

⇒ *Tests Domain 2: Attention / working memory*

The revised version of the d2 Test [60] is a psychological test that assesses attention and concentration. It consists of the letters “d” and “p” with one to four dashes arranged either above or below the letter. These letters are arranged in 14 rows of 47 characters on an A4 sheet of paper.

The examinee is asked to identify and cross out all “d’s” with two dashes. These are known as ‘target signs’. Crossing one out gives the examinee a point. A non-target sign is a “d” with more or less than two dashes or any kind of “p”. These should not be crossed out and leads to one less point if done so. Skipping or forgetting to cross out a target sign also results in point reduction. The subject should always work from left to right. Corrections are permitted. This is a timed test, as the examiner only gives 20 seconds for each row of signs to be completed. After this time the examinee continues looking for target signs in the next row without the possibility to revise previously completed signs.

The examiner encourages the subject to work as quickly, carefully and with as much concentration as possible. After performing a practice row where the examiner makes sure that the instructions have been understood, the test is initiated and the examiner tells the examinee to move on to the next row of characters after every 20 seconds.

Scoring: The final score is calculated by subtracting all non-target signs and skipped target signs from the correctly marked target signs. This score is known as KL-Score, an abbreviation from the German word *Konzentrationsleistung*, meaning concentration performance.

2.4.2. 7. Colour-Word-Interference Test

⇒ *Tests Domain 3: Executive function / abstraction*

This version is a 1989 German adaptation by Wolfram [61] from the original test designed by Stroop in 1935. It assesses the ability to suppress a highly automated response pattern in favour of a new one requiring an optimised behavioural controlled cognitive process. The more difficult it is for the individual to suppress such well learned − almost intrinsic − action in favour of a new response, the stronger its interference tendency. This test is an indication of the examinee’s executive function.

The test consists of an A4 sheet with 10 rows of 10 written colour names where the name and the colour never match. The colour and the word change from item to item. The subject will be asked to name the colour in which each item is printed (but not the written word). If the examinee makes a mistake he is informed so he can try again. The final score will be the total time needed in seconds to complete all the items.

2.4.2. 8. Controlled Oral Word Association Test (COWA), Subtest S-Words and Subtest Animals

⇒ *Tests Domain 1: Language/verbal fluency*

Also known in Germany as the *Regensburger Verbal Fluency Test* [62], this is a verbal fluency test that measures spontaneous production of words beginning with a designated letter or belonging to the same category.

The subject is asked to name as many words belonging to a certain category in two minutes. When testing phonologic verbal fluency, the subject is asked to name as many words starting with the letter "S" in two minutes, avoiding proper nouns. When testing semantic verbal fluency, he is asked to name as many animals in the same amount of time. The examiner writes down the words to avoid repeated answers.

Scoring: one point is obtained for each correct word.

2.4.2. 9. Trail Making Test (TMT) [63-65]

⇒ *Tests Domain 2: Attention / working memory* (Part B)

⇒ *Tests Domain 3: Executive function / abstraction* (Part B)

⇒ *Tests Domain 5: Speed of information processing* (Part A)

Part A of the Trail Making Test requires the subject to connect numbers 1 though 25 randomly arranged on an A4 page in increasing order. This assesses their speed of information processing.

In Part B there are 25 encircled numbers and letters that have to be connected in alternating and increasing order. This test evaluates cognitive flexibility and ability to maintain a complex response as well as attention and working memory.

Scoring: The time in seconds needed to complete each part of the test, resulting in two different scores.

2.4.2. 10. Wechsler Adult Intelligence Scale (WAIS-III), Subtest Digit Symbol-Coding

⇒ *Tests Domain 5: Speed of information processing*

This subtest of the WAIS-III battery [66] consists of an A4 sheet of paper with several numbers and a caption with the translation of numbers into symbols. Under each digit the subject writes down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (120 seconds) is recorded. Information processing speed is mainly evaluated, as well as incidental learning by continuously repeated copying.

2.4.2. 11. Grooved Pegboard

⇒ *Tests Domain 7: Motor skills*

The Grooved Pegboard [67, 68] is an easy to administer test which assesses motor impairment. It consists of a metal board with a matrix of 25 holes with randomly positioned slots. Pegs have a ridge along one side and must be rotated to match the hole before they can be inserted. The patient's task is to insert the metal pegs as quickly as possible into the slots in sequence until all pegs have been placed, first with the dominant hand and then with the non-dominant one. The score is the time needed in seconds to complete the task with each hand.

2.5 Statistical analysis

Descriptive statistics were used to compare characteristics between groups of individuals. All normally distributed continuous variables were reported as means and standard deviation of the mean (SD). All non-normally distributed continuous variables were reported as medians with interquartile ranges (IQR). Associations of categorical variables

between the different groups and analysed factors were assessed using the chi-square test. The direction of the association was obtained by using the Goodman and Kruskal's gamma test. For non-normally distributed variables with two samples, the Mann-Whitney U Test was used. For normally distributed and non-normally distributed continuous variables with more than two samples, the ANOVA and the Kruskal–Wallis one-way analysis of variance tests were used, respectively. The relationship between two variables was evaluated by linear correlation analysis. For samples with normal distribution the Pearson correlation coefficient was applied. For nonparametric samples, Spearman's rho coefficient was used. The intensity of the association between a categorical and a quantitative variable was assessed using Cohen's d association index. All p-values were 2-tailed and considered significant at $p < 0.05$. The optimal cut-off point for the screening test to maximise sensitivity and specificity was assessed by a Receiver Operating Characteristic (ROC) curve. The analyses were performed using IBM SPSS Statistics version 22.0.

Sensitivity, specificity, predictive values and Youden's J-Index were calculated using a Microsoft Excel spreadsheet provided by The Critical Appraisal Skills Programme (CASPe), which is available on-line at redcaspe.org.

CHAPTER THREE: RESULTS

The results will be described in five sections. Firstly, the focus will be on the total number of participants who were screened with the International HIV Dementia Scale. Secondly, the results of the sample of participants who completed neuropsychological testing will be described. Thirdly, the results obtained in the neuropsychological battery of tests will be presented. Fourthly, the prevalence of HAND in our cohort will be evaluated following the Frascati criteria, allowing, finally, to calculate the sensitivity, specificity and accuracy of the screening tool.

3.1 Results of the screening process

Between July 2010 and April 2012, 510 patients were screened for HIV-associated neurocognitive disorders using the International HIV Dementia Scale. There were 480 HIV-positive patients and 30 were HIV-negative controls. The vast majority of participants were men (491; 96.3%). The ages ranged between 19 and 80 years old, the median age being 39 (IQR 31-46). Increasing age was found to be associated with lower scores in the IHDS ($p < 0.001$). Analysis by gender did not show any differences between groups.

Overall, 278 participants (54.5%) scored 12 points. Therefore, more than half of the screened population achieved the maximum obtainable score in the three subtests that make up the IHDS. Continuing in descending order, 66 participants (12.9%) scored 11.5 points, and 76 participants (14.9%) scored 11 points. Only 11 participants (2.2%) scored 10.5 points, and 49 participants (9.6%) obtained a score of 10 points or less. Of these, the majority (41; 8%) had between 9 and 10 points. Only a very small group of 8 participants (1.6%) obtained a score of less than 9 points. The remaining 30 participants (5.9%) were HIV-negative participants with scores between 11.5 and 12 that formed the control group. Figs. 3.1 and 3.2 illustrate these results. Table 3.1 summarises the participant's general characteristics.

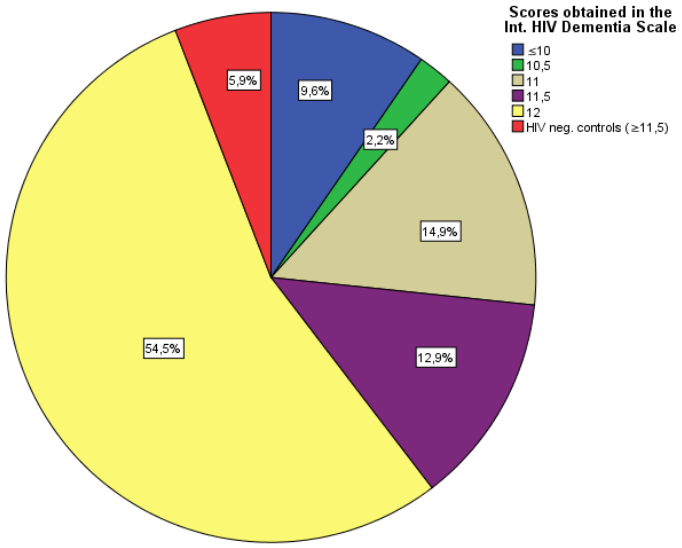

Fig. 3.1 – Frequencies of obtained scores in the International HIV Dementia Scale (IHDS)

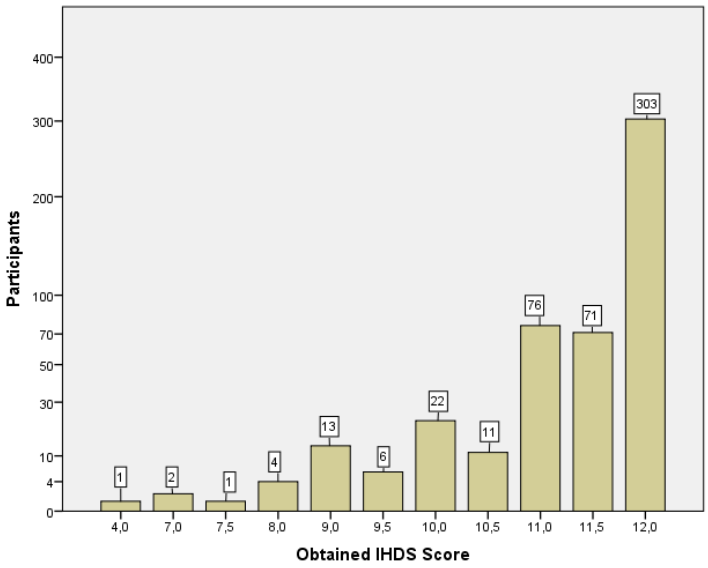

Fig. 3.2 – Number of participants distributed by IHDS score obtained

The median duration of the HIV infection was 56 months. This time was twice as long in the group with scores ≤10 compared with the groups who scored 11.5 or 12. The median nadir in $CD4^+$ cell count continuously increased from 200 cells/µL in the ≤10 points group to 287 cells/µL in the group with score = 12. This difference was found to be significant at the 0.002 p-level. There were no differences between groups in the current $CD4^+$ cell count. Most of the participants (67%) were on an antiretroviral treatment. This percentage was higher in those who obtained a lower score. The CPE-score median was 7 in all the groups and had little variation in range and means. There were no significant differences related to the use of efavirenz or coinfection with hepatitis C among the groups analysed.

When analysing the answers given in the DNAA questionnaire, significant differences between the groups were found. The group who achieved ≤10 points in the IHDS, reported between two and three times more depression, concentration, motor and sleeping problems than the participants with higher IHDS scores. Patients who were being treated with cART reported more subjective neurocognitive limitations, especially in concentration and fine motor skills (see Fig. 3.3).

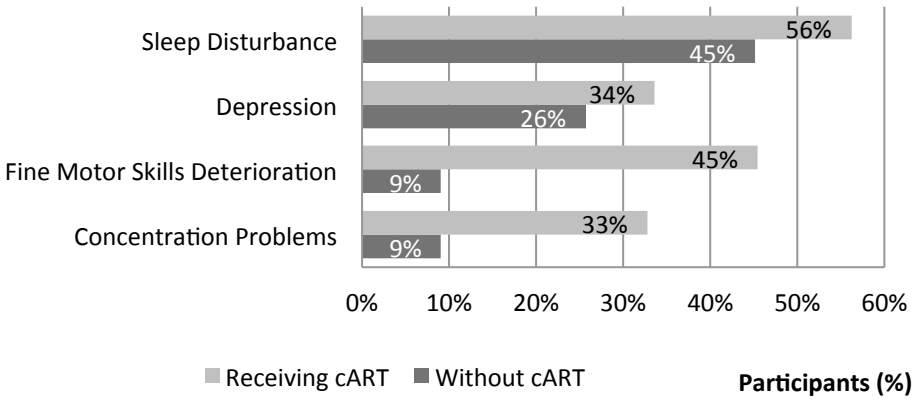

Fig. 3.3 – Participants reporting cognitive complaints in the DNAA questionnaire, sorted by therapy status.

We also compared the participant's serological status versus the median scores obtained in the different subtests of the IHDS. HIV-positive participants obtained lower scores in the psychomotor subtest (z -2.43; $p = 0.015$), whereas memory (word recall) or motor speed (finger tapping) did not show significant differences between the groups.

We conducted a bivariate correlation analysis between possible risk factors and their effect on the answers given in the DNAA questionnaire and the scores obtained in the IHDS. Firstly, patients who reported suffering from a subjective neurocognitive limitation on the questionnaire (sleep disturbance; depression; fine motor skills deterioration; concentration problems), often suffered from more than one ($r = 0.50$; $p < 0.001$). Secondly, experiencing fine motor problems correlated better with a lower score in the IHDS than any other listed on the questionnaire ($r = -0.31$; $p < 0.001$). Finally, older participants tended to get lower scores in the IHDS ($r = -0.31$; $p < 0.001$). Smaller correlations were also found between a lower IHDS score and a lower $CD4^+$ nadir ($r = 0.20$; $p < 0.001$) and a longer duration of the HIV infection ($r = -0.20$; $p < 0.001$). No relevant correlations were found between the IHDS score and the current $CD4^+$ cell count, the current viral load, the viral load zenith, gender, hepatitis C coinfection or the use of antiretrovirals, including efavirenz.

Table 3.1: Group characteristics, scores obtained in the Int. HIV Dementia Scale (IHDS) and answers given in DNAA questionnaire (sorted by score obtained)

		All screened	*IHDS ≤10*	*IHDS = 10.5*	*IHDS = 11*	*IHDS = 11.5*	*IHDS = 12*	*HIV neg. contr.*	*P - Value*
Demographics	Participants, n *(%)*	510 *(100%)*	49 *(9.6%)*	11 *(2.2%)*	76 *(14.9%)*	66 *(12.9%)*	278 *(54.5%)*	30 *(5.9%)*	--
	Female, n *(%)*	19 *(3.7%)*	1 *(2%)*	0	3 *(3.9%)*	6 *(9.1%)*	8 *(2.9%)*	1 *(3.3%)*	0.245
	Age range	19-80	26-71	23-61	22-72	19-66	19-80	23-56	--
	Age, median *(interquartile range)*	39 *(31-46)*	49 *(40-58)*	44 *(30-57)*	43 *(35-51)*	40 *(33-46)*	36 *(29-43)*	40 *(30-49)*	**< 0.001**
HIV infection	Months since testing HIV-positive, median	56	108	69	69	53	46	--	**0.004**
	Current $CD4^+$ count, range	15-1595	139-1038	258-971	36-1131	120-1463	15-1595	--	--
	Current $CD4^+$ count, median	497	467	641	446	484	515	--	0.223
	Historical $CD4^+$ nadir, range	2-777	2-523	24-641	6-578	13-756	3-777	--	--
	Historical $CD4^+$ nadir, median	259	200	292	219	241	287	--	**0.002**
cART information	Patients receiving cART, n *(%)*	321 *(67%)*	39 *(79.6%)*	8 *(72.7%)*	56 *(73.7%)*	47 *(71.2%)*	169 *(60.8%)*	--	**0.034**
	Current CPE-Score, range	3-13	3-13	7-10	6-10	3-10	4-11	--	--
	Current CPE-Score, mean *(SD)*	7.28 *(1.08)*	7.41 *(1.73)*	7.63 *(1.06)*	7.46 *(0.87)*	7.13 *(0.97)*	7.21 *(0.99)*	--	0.222
	cART includes efavirenz, n *(%)*	60 *(11.8%)*	4 *(8.16%)*	1 *(9.1%)*	6 *(10.5%)*	10 *(15.2%)*	37 *(13.3%)*	--	0.769
	Hepatitis C coinfection, n *(%)*	33 *(6.5%)*	2 *(4.1%)*	1 *(9.1%)*	7 *(9.2%)*	4 *(6.1%)*	19 *(6.9%)*	--	0.846
IHDS subtest scores	Motor Speed Subtest, mean score*(SD)*	3.94 *(0.27)*	3.51 *(0.65)*	4	3.92 *(0.27)*	4	4	4	-
	Psychomotor Speed Subtest, mean score*(SD)*	3.79 *(0.55)*	2.57 *(0.50)*	3.45 *(0.52)*	3.59 *(0.46)*	4	4	4	-
	Memory (Recall) Subtest, mean score *(SD)*	3.75 *(0.46)*	3.13 *(0.83)*	3.05 *(0.52)*	3.49 *(0.50)*	3.5	4	3.92 *(0.19)*	-
	Total Score, mean *(SD)*	11.48 *(0.91)*	9.21 *(1.12)*	10.5	11	11,5	12	11.9 *(0.18)*	-
DNAA answers	Reported concentration problems, n *(%)*	121 *(23.7%)*	28 *(57.2%)*	4 *(36.4%)*	13 *(17.1%)*	15 *(22.7%)*	59 *(21.2%)*	2 *(6.7%)*	**<0.001**
	Reported motor problems, n *(%)*	67 *(13.1%)*	24 *(49%)*	0	8 *(10.5%)*	4 *(6.1%)*	30 *(10.8%)*	1 *(3.3%)*	**<0.001**
	Feels depressed, n *(%)*	134 *(26.3%)*	25 *(51%)*	3 *(27.3%)*	25 *(32.9%)*	15 *(22.7%)*	66 *(23.7%)*	0	**<0.001**
	Reported sleeping problems, n *(%)*	247 *(48.4%)*	40 *(81.6%)*	3 *(27.2%)*	41 *(53.9%)*	24 *(36.4%)*	134 *(48.2%)*	5 *(17%)*	**<0.001**

3.2 Characteristics of the sample that completed neuropsychological assessment

The neuropsychological evaluation took place between April 2012 and July 2014. We selected a sample of 90 HIV-positive participants, who were divided into three groups of 30 participants depending on their score. Thirty HIV-negative patients formed the control group. The group's characteristics are summarised in Table 3.2. Once again, the majority of participants were men (98.3%), with a median age of 43 (IQR 35-51) years old. The mean education − evaluated in total years of attending a teaching institution − was 16 (IQR 14-18). There were no significant differences in age or education between the groups.

The median duration of the HIV-infection was 83 months. The participants with poor performance in the IHDS had lived with the virus for a longer time (152 months) than those with average (89 months) or high (53 months) performance. Once again, the median $CD4^+$ nadir was directly related to the score obtained in the IHDS: participants with a poor performance had lower nadir rates (209 cells/µL) than those with a high performance (324 cells/µL). The current $CD4^+$ cell count at the time of neuropsychological testing did not reveal any differences between groups.

Most participants (89%) were receiving antiretroviral therapy. The proportion of treated participants was smaller in the high performance group: 77% vs. 93% in the poor and 97% in the average performance groups. With a median of 7, the CPE score did not vary much between study groups. There were no differences regarding the use of efavirenz or a hepatitis C coinfection, and no significant correlations were found between these risk factors and the development of HAND.

HIV-positive participants reported more cognitive complaints in the DNAA questionnaire than the HIV-negative controls (90% in low vs. 20% in average and 27% in high performance groups; 7% HIV-negative controls). Reporting concentration problems also showed a negative effect on the obtained IHDS score ($d = -1{,}46$; $p < 0.001$).

Participants who were HIV-positive obtained lower scores in all three subtests of the IHDS compared to the negative controls. This correlation was strongest in the

psychomotor subtest (z -3.99; $p < 0.001$), followed by the memory (word recall) subtest ($z = -3.34$; $p = 0.001$) and the motor speed (finger tapping) subtest ($z = -2.89$; $p = 0.004$).

Again, a bivariate correlation analysis was performed between the possible risk factors that may influence HAND and the screening and diagnostic outcome. Here we observed that the older the participant was, the lower the score obtained in the screening ($r = 0.22$; $p = 0.015$). This same correlation was also found in respect to the $CD4^+$ cell count nadir ($r = 0.25$; $p = 0.003$). In addition, participants who were being treated with antiretrovirals had lower screening scores ($r = 0.22$; $p = 0.037$). Similarly, participants with a lower CD4+ nadir had higher HAND incidence ($r = 0.28$; $p = 0.009$). Education, measured as years attending a teaching institution, showed to correlate with the diagnostic outcome even after applying demographic corrections: The less educated the participants were, the greater the risk of developing the disease, especially of the more severe forms ($r = 0.35$; $p < 0.001$). No further relevant correlations were found with the current $CD4^+$ cell count, the current viral load, the viral load zenith, gender, hepatitis C coinfection or the use of efavirenz.

3.3 Outcome of the neuropsychological assessment

The results obtained in the different subtests of the neuropsychological battery can be seen in Table 3.3. All results are expressed as standard scores (z-scores). The standard score is the number of standard deviations (SD) an observation is above or under the mean. The mean is represented by the number 0. Thus, a positive standard score indicates a result above the mean, while a negative standard score indicates a result below the mean. This score results from the adjustment for age and education of the obtained raw score in each individual subtest. This is mainly done to quantify the performance for each of the neuropsychological tests in an equivalent way without being influenced by distracting factors.

Table 3.2: Group characteristics, scores obtained in the Int. HIV Dementia Scale (IHDS) and answers given in DNAA questionnaire (sorted by study group)

Observations			*All groups*	*Poor Performance*	*Average Performance*	*High Performance*	*Control*	*P – Value*
Poor Performance: Participants with IHDS scores of 10 or less. *Average Performance:* Participants with IHDS scores of 10.5 or 11. *High Performance:* Participants with IHDS scores of 11.5 or 12. *Control*: HIV-negative participants with IHDS scores of 11.5 or 12.	Demographics	Participants, n *(%)*	120 *(100%)*	30 *(25%)*	30 *(25%)*	30 *(25%)*	30 *(25%)*	--
		Female, n *(%)*	2 *(1.7%)*	0	0	1 *(3.3%)*	1 *(3.3%)*	0.565
		Age range	23-62	25-62	28-59	23-57	23-56	--
		Age, median *(interquartile range)*	43 *(35-51)*	45 *(39-51)*	46*(38-54)*	41 *(33-49)*	40 *(31-49)*	0.129
		Education, in years, median *(interquartile range)*	15 *(13-17)*	15 *(13-15)*	16 *(14-18)*	16 *(15-17)*	16 *(15-17)*	0.587
	HIV infection	Months since testing HIV-positive, median	83	142	89	53	--	**0.025**
		Current $CD4^+$ count, range	139-1252	173-1252	154-1246	139-1064	--	--
		Current $CD4^+$ count, median	554	556	548	577	--	0.610
		Historical $CD4^+$ nadir, range	0-565	2-441	0-555	40-565	--	--
		Historical $CD4^+$ nadir, median	274	209	282	324	--	**0.036**
	cART information	Patients receiving cART, n *(%)*	80 *(89%)*	28 *(93%)*	29 *(97%)*	23 *(77%)*	--	**0.031**
		Current CPE-Score, range	3-12	3-12	4-10	7-9	--	--
		Current CPE-Score, mean *(SD)*	7.25 *(1.12)*	7.07 *(1.39)*	7.34 *(1.14)*	7.35 *(0.65)*	--	0.238
		cART includes efavirenz, n *(%)*	7 *(7.7%)*	2 *(6.6%)*	2 *(6.6%)*	3 *(10%)*	--	0.856
		Hepatitis C coinfection, n *(%)*	3 *(3.3%)*	1 *(3.3%)*	1 *(3.3%)*	1 *(3.3%)*	--	0.990
	IHDS subtest scores	Motor Speed Subtest, mean score*(SD)*	3.79 *(0.48)*	3.3 *(0.70)*	3.87 *(0.34)*	4	4	-
		Psychomotor Speed Subtest, mean score*(SD)*	3.62 *(0.66)*	2.83 *(0.79)*	3.63 *(0.49)*	4	4	-
		Memory (Recall) Subtest, mean score*(SD)*	3.62 *(0.57)*	3.22 *(0.76)*	3.44 *(0.57)*	3.9 *(0.20)*	3.92 *(0.19)*	-
		Total Score, mean *(SD)*	11.04 *(1.17)*	9.38 *(1.01)*	10.94 *(0.17)*	11.93 *(0.17)*	11.9 *(0.18)*	-
	DNAA answers	Reported concentration problems, n *(%)*	43 *(35.8%)*	27 *(90%)*	6 *(20%)*	8 *(26.7%)*	2 *(6.7%)*	**<0.001**
		Reported motor problems, n *(%)*	13 *(10.8%)*	11 *(36.7%)*	0	1 *(3.3%)*	1 *(3.3%)*	**<0.001**
		Reported sleeping problems, n *(%)*	37 *(30.8%)*	17 *(56.7%)*	5 *(16.7%)*	10 *(33.3%)*	5 *(17%)*	**0.002**

The mean scores on all subtests were significantly different among the four study groups. In the low performance group, the scores varied between +0.2 and -1.29 SD. In five tests (TMT Part A, TMT Part B, Verbal Learning: Delayed Recall, Language: S-Words and d2-Test) the results were substantially lower for this group, with mean scores near or under -1 SD. Three of these five tests have a special significance as they showed a clear trend among the different study groups, as shown in Fig. 3.4.

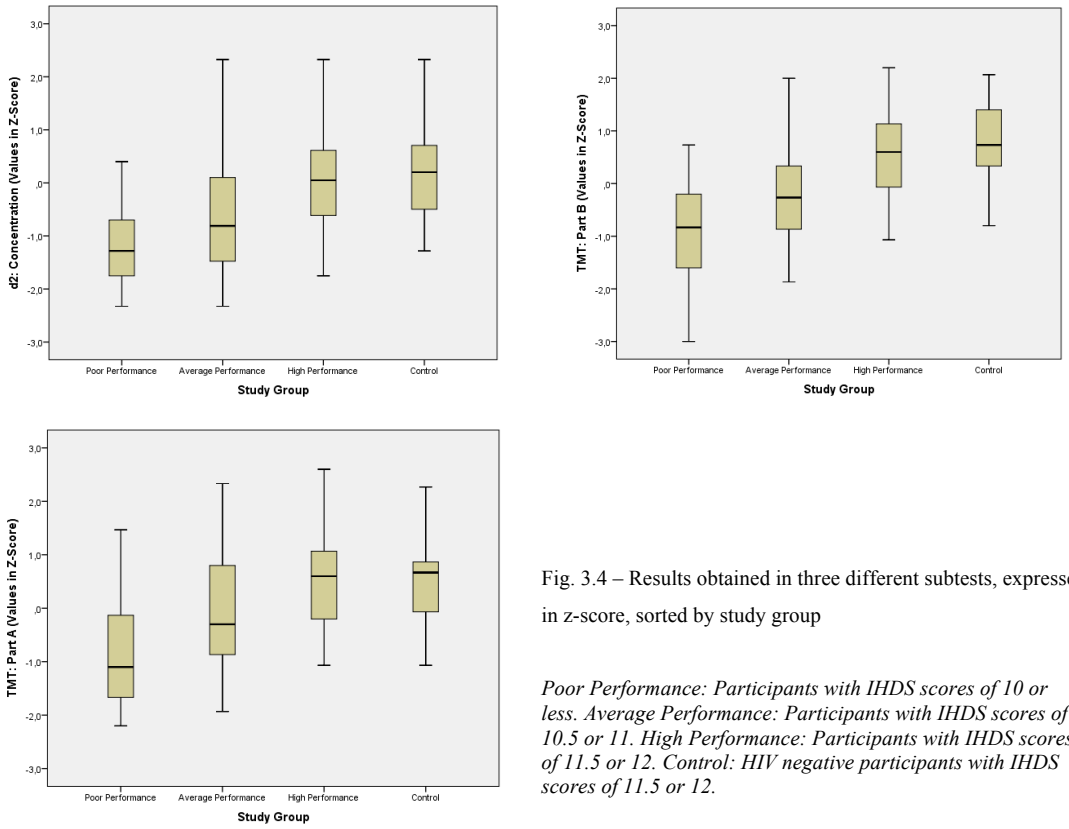

Fig. 3.4 – Results obtained in three different subtests, expressed in z-score, sorted by study group

Poor Performance: Participants with IHDS scores of 10 or less. Average Performance: Participants with IHDS scores of 10.5 or 11. High Performance: Participants with IHDS scores of 11.5 or 12. Control: HIV negative participants with IHDS scores of 11.5 or 12.

In the average performance group, mean scores are between -0.72 and +0.83 SD. In the high performance group, mean scores range between -0.31 and +1.06 SD: here, most scores are above zero (except in two cases - Visual Learning: identifying and Language: S-Words), and one subtest (Digit Span: forwards) even surpasses the +1 SD threshold.

In the control group, the mean scores range from -0.4 to +1.7 SD. This group has relatively higher scores than the high performance group. However, after performing an ANOVA test for comparison of means between the two groups, these differences were not significant.

Table 3.3: Scores obtained in the different tests included in the neuropsychological battery, sorted by study group (all scores expressed as z-scores)							
Observations		*All groups*	*Poor Performance*	*Average Performance*	*High Performance*	*Control*	*P - Value*
Poor Performance: Participants with IHDS scores of 10 or less. *Average Performance:* Participants with IHDS scores of 10.5 or 11. *High Performance:* Participants with IHDS scores of 11.5 or 12. *Control*: HIV-negative participants with IHDS scores of 11.5 or 12.							
	Participants, n *(%)*	120 *(100%)*	30 *(25%)*	30 *(25%)*	30 *(25%)*	30 *(25%)*	--
	Verbal Learning: Total Score, mean *(SD)*	-0.10 (0.89)	-0.66 *(0.9)*	-0.29 *(0.87)*	0.23 *(0.70)*	0.32 *(0.72)*	**<0.001**
	Verbal Learning: Immediate Recall, mean *(SD)*	-0.11 *(1.04)*	-0.74 *(0.91)*	-0.08 *(1.06)*	0.01 *(0.98)*	0.35 *(0.98)*	**<0.001**
	Verbal Learning: Delayed Word Recall, mean *(SD)*	-0.25 *(1.02)*	-0.97 *(0.73)*	-0.33 *(0.92)*	0.06 *(0.95)*	0.25 *(1.05)*	**<0.001**
	Verbal Learning: Identifying, mean *(SD)*	-0.12 *(0.99)*	-0.73 *(0.93)*	-0.16 *(0.96)*	0.08 *(1.05)*	0.35 *(0.72)*	**<0.001**
	Visual Learning: Total Score, mean *(SD)*	0.02 *(0.78)*	-0.52 *(0.86)*	0.10 *(0.66)*	0.13 *(0.63)*	0.37 *(0.72)*	**<0.001**
	Visual Learning: Identifying, mean *(SD)*	-0.19 *(0.51)*	-0.53 *(0.78)*	-0.03 *(0.18)*	-0.13 *(0.35)*	-0.07 *(0.37)*	**<0.001**
	ROCF: Immediate Recall, mean *(SD)*	0.72 *(1.30)*	-0.07 *(1.47)*	**0.83 *(1.10)***	0.84 *(1.16)*	**1.27 *(1.10)***	**<0.001**
ROCF: Rey-Osterrieth Complex Figure Test *TMT:* Trail Making Test *LPS-UT3:* Horn's Performance Test System, Subtest 3 **Bold:** minimum and maximum mean scores in each study group.	ROCF: Delayed Recall, mean *(SD)*	0.70 *(1.36)*	-0.06 *(1.54)*	0.81 *(1.22)*	0.84 *(1.28)*	1.20 *(1.08)*	**0.002**
	Digit Span: Forwards, mean *(SD)*	**0.74 *(1.02)***	**0.20 *(1.24)***	0.70 *(0.88)*	**1.06 *(0.94)***	0.99 *(0.78)*	**0.003**
	Digit Span: Backwards, mean *(SD)*	0.44 *(1.13)*	-0.33 *(0.99)*	0.14 *(1.03)*	0.83 *(1.04)*	1.11 *(0.87)*	**<0.001**
	d2-Test: Concentration , mean *(SD)*	-0.44 *(1.06)*	**-1.29 *(0.76)***	-0.65 *(1.16)*	-0.02 *(0.86)*	0.15 *(0.86)*	**<0.001**
	Stroop Colour Test, mean *(SD)*	0.03 *(1.17)*	-0.85 *(1.26)*	-0.10 *(1.00)*	0.60 *(0.86)*	0.48 *(0.97)*	**<0.001**
	Language: S-Words, mean *(SD)*	**-0.63 *(0.88)***	-1.07 *(1.01)*	**-0.72 *(0.75)***	**-0.31 *(0.90)***	**-0.40 *(0.65)***	**0.003**
	Language: Animals, mean *(SD)*	-0.14 *(1.14)*	-0.67 *(1.29)*	-0.32 *(1.16)*	0.31 *(1.12)*	0.12 *(0.69)*	**0.003**
	TMT: Part A, mean *(SD)*	0.05 *(1.08)*	-0.90 *(0.98)*	0.09 *(1.08)*	0.49 *(0.83)*	0.52 *(0.80)*	**<0.001**
	TMT: Part B, mean *(SD)*	0.04 *(1.10)*	-0.95 *(0.96)*	-0.16 *(0.99)*	0.55 *(0.80)*	0.73 *(0.76)*	**<0.001**
	Grooved Pegboard: Dominant Hand, mean *(SD)*	-0.01 *(0.60)*	-0.40 *(0.81)*	-0.03 *(0.49)*	0.17 *(0.38)*	0.23 *(0.43)*	**<0.001**
	Grooved Pegboard: Non-Dom. Hand, mean *(SD)*	0.05 *(0.68)*	-0.43 *(0.90)*	0.07 *(0.52)*	0.27 *(0.45)*	0.30 *(0.54)*	**<0.001**
	Digit Symbol Test, mean *(SD)*	-0.21 *(1.03)*	-0.73 *(0.79)*	-0.32 *(0.95)*	0.07 *(1.10)*	0.16 *(1.06)*	**0.002**
	LPS-UT3: Fluid Intelligence, mean *(SD)*	0.71 *(0.93)*	0.08 *(0.97)*	0.56 *(0.89)*	1.13 *(0.70)*	1.06 *(0.77)*	**<0.001**

The lowest average score was recorded in the poor performance group in the d2-Test (-1.29 SD). The highest average score was recorded in the control group in the ROCF: Immediate Recall test (+1.27 SD).

After conducting an analysis of correlation between the different subtests of the battery and the result obtained in the screening, the highest correlation was found with the TMT Part B subtest (r = 0.552), followed by the Digit Span Backwards (r = 0.533), the TMT Part A (r = 0.514) and the d2-Test (r = 0.499). All correlations were significant at the $p < 0.001$ level.

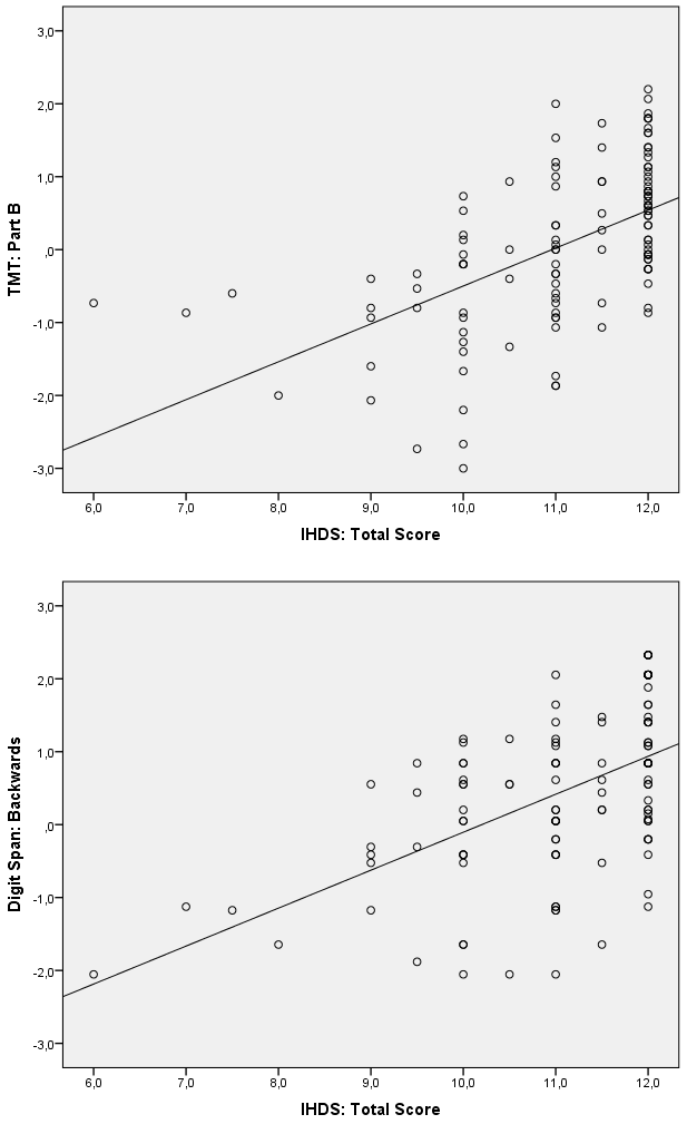

Fig. 3.5 – Correlation of the IHDS total score and the TMT Part B and Digit Span Backwards subtests.

3.4 Prevalence of HAND

The participants' performance on the neurocognitive assessment and their subjective responses provided in the DNAA questionnaire were used for diagnosing HAND according to the Frascati criteria [18]. From the 90 evaluations performed, the total number of HAND cases found was 57. Of these, 23 were ANI cases, 17 cases of MND and 17 were cases of HAD. The remaining 33 participants obtained a normal neuropsychological evaluation, and were considered to be neurocognitively normal (NCN).

This observed prevalence of 57 detected cases of 90 performed evaluations had to be adjusted due to the stratification of participants -the selection of the three subsamples- done in the second part of the study. Therefore, we performed a weighted sum of the HAND cases in each group multiplied by their relative weight over the total of the screened population. This is used when the different values of a data set have a different relative weight compared to other values. For this purpose we used the following formula [69]:

$$\text{Adjusted Prevalence} = \frac{1}{N}\,\Sigma i\,\frac{(e_i \cdot n_i)}{m_i}$$

where e_i = number of detected ANI, MND or HAD cases in one study group; n_i = total number of screened participants in one stratification group; m_i = size of study group (always 30); N = total size of the global screened population (always 480).

Following this adjustment, the overall prevalence of HAND in our cohort was 43%: 20% were classified as ANI, 17% as MND and 6% as HAD. The remaining 57% were considered NCN. . In the control group, we found three cases (10%) with criteria compatible with ANI, and the rest were NCN (90%).

Sorted by study group, the total number of HAND was: poor performance (n = 29; 97%); average performance (n = 19; 63%); high performance (n = 9; 30%); controls (n = 3; 10%). For the better understanding of the results, we applied the same diagnostic criteria to the control group, even though these do not strictly apply to HIV-negative individuals. In this case, the concept HAND is used as a synonym for neurocognitively impaired (NCI), which is more appropriate.

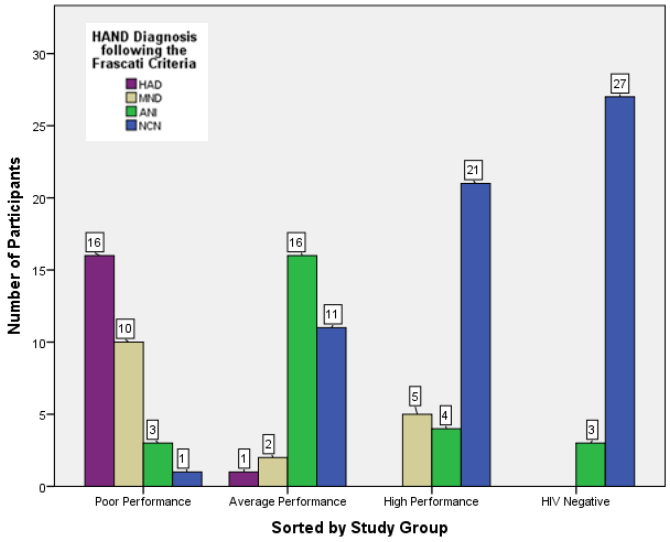

Fig. 3.6 – Prevalence of HAND subtypes, sorted by study group

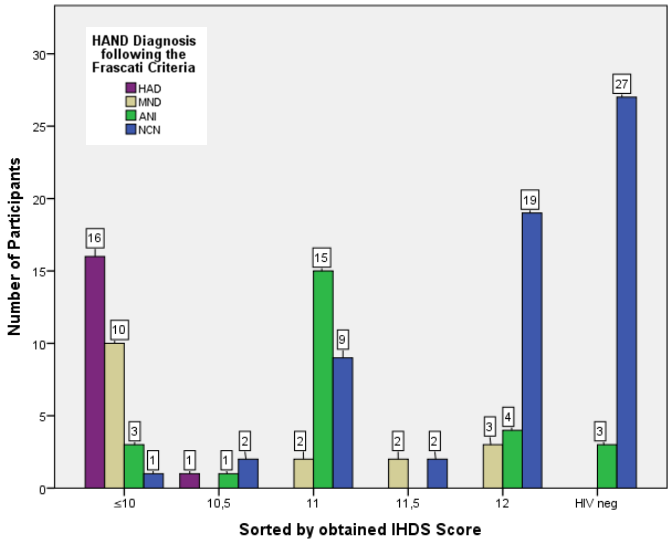

Fig. 3.7 – Prevalence of HAND subtypes, sorted by obtained IHDS score

As seen in Fig. 3.6 and 3.7, the cases of the more severe form of HAND, HIV-associated dementia (HAD), were concentrated almost entirely in the poor performance group. Here, it achieved an in-group prevalence of 53%. This group included all participants with an IHDS score of 10 or less. There was also one participant in the average performance group diagnosed with HAD, who had

previously obtained a score of 10.5 points in the screening test. There were no cases of HAD reported in the high performance or control groups.

Cases of mild neurocognitive disorder (MND) were found in the three study groups with HIV-positive participants. The highest prevalence was found in the poor performance group (n=10; 33%), followed by the high performance (n=5; 17%) and the average performance group (n=2; 7%). The control group did not record any case of MND.

Cases of asymptomatic neurocognitive impairment (ANI) were found in all study groups, including the control group. The majority were diagnosed in the average performance group (n=16; 53%). This group consisted of participants who scored between 10.5 and 11 in the IHDS. The remaining three groups each had between 3 and 4 cases of ANI, which represents 10 to 13% of the in-group prevalence.

The number of participants with a normal neurocognitive outcome increased along with the score obtained in the IHDS. Whereas in the poor performance group only one participant (3%) was NCN, the rate increased to 11 participants (37%) in the average performance group and to 21 participants (70%) in the high performance group. In the control group, 27 participants (90%) were NCN. The difference in NCN count between high performance and control groups was found to be at the limit of non-significance (p = 0.053).

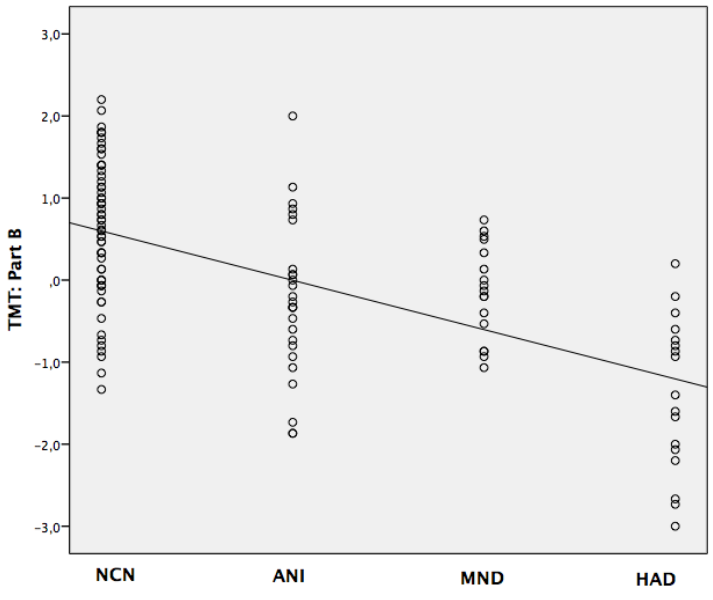

Fig. 3.8 – Correlation of the HAND diagnosis and the Trail Making Test (TMT) Part B subtest.

NCN: neurocognitively normal; ANI: asymptomatic neurocognitive impairment; MND: mild neurocognitive impairment; HAD: HIV-associated dementia.

The subtest that best correlated with the diagnostic of HAND was the TMT Part B (r = 0.602), followed by the d2-Test (r = 0.599), the TMT Part A (r = 0.506), the Visual Learning (r = 0.505) and the ROCF immediate recall (r = 0.500). All correlations were significant at the $p < 0.001$ level.

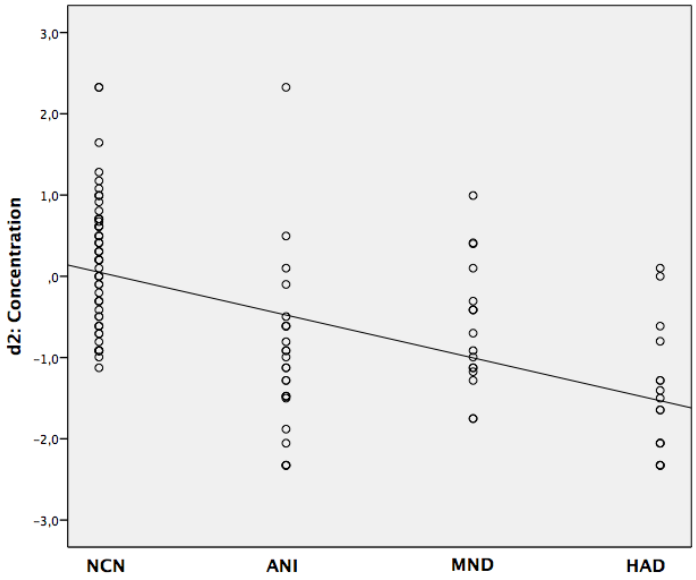

Fig. 3.9 – Correlation of the HAND diagnosis and the d2 Concentration subtest.

NCN: neurocognitively normal; ANI: asymptomatic neurocognitive impairment; MND: mild neurocognitive impairment; HAD: HIV-associated dementia.

3.5 Calculation of sensitivity, specificity and accuracy of the IHDS

The diagnostic efficacy of the IHDS was assessed using a Receiver Operating Characteristic (ROC) curve analysis. This statistical test allows us to determine the optimal cut-off value for the IHDS when screening for HAND. This should correspond with the value where both sensitivity and specificity are highest. To assess this calculation we used the data from all performed evaluations (90 in HIV positive plus 30 in HIV negative), being 60 (57 + 3) the total cases of HAND. The calculated area under the ROC curve (AUC) was 0.843 ($p < 0.001$). This indicated that the IHDS was a fairly useful test with a good balance of sensitivity and specificity, and supported the test's accuracy for diagnosing HAND.

We also calculated Youden's Index for diagnostic accuracy, or J-Index [70], which is a statistical test that captures the performance of a diagnostic test as a single number. This is defined by the formula $J = Sensitivity + Specificity - 1$, and its value ranges from 0 to 1. When a diagnostic test gives the same proportion of positive results for

groups with and without the disease − meaning that the screening test is useless − its value is 0. When a diagnostic test indicates that there are no false-positives or false-negatives − meaning that the screening test is perfect − the value equals 1. The sensitivity, specificity, predictive values and J-Index for the different cut-offs can be seen on Table 3.4.

Table 3.4: Characteristics of the different cut-off values for HAND on the IHDS

Cut-Off	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*J-Index*
9.5	22%	100%	100%	56%	0.2
10	48%	98%	97%	66%	0.5
10.5	52%	95%	91%	66%	0.5
11	80%	80%	80%	80%	0.6
11.5	83%	68%	72%	80%	0.5
12	100%	0%	50%	100%	0.0

It was also of interest to determine whether the cut-off value and the accuracy change when looking for the more severe cases of HAND only − the cases of HAD solely – excluding the cases of MND and ANI. We repeated the same procedure, this time screening for HAD cases only. These results can be seen on Table 3.5.

Table 3.5: Characteristics of the different cut-off values for HAD only on the IHDS

Cut-Off	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*J-Index*
9.5	47%	95%	62%	92%	0.4
10	94%	86%	53%	98%	0.8
10.5	100%	84%	50%	100%	0.8
11	100%	58%	28%	100%	0.6
11.5	100%	50%	25%	100%	0.5
12	100%	0%	14%	100%	0.0

A global analysis of the results and their implications is discussed in the next chapter.

CHAPTER FOUR: DISCUSSION

4.1. Commentary on the IHDS: Sensitivity, specificity, accuracy and applicability

To date, there has been no standardisation of an internationally used screening tool for HAND in a German speaking population. The main objective of this study was to set an appropriate cut-off value for the IHDS when screening for HAND in this specific population.

One of the fundamental qualities a screening tool is expected to have is high sensitivity, in order to detect as many affected individuals as possible while minimising false-negative results. To determine which cut-off value achieves the highest sensitivity, we performed a Receiver Operating Characteristic curve analysis in the previous chapter. The results of this analysis (Table 3.4) the IHDS was 80% sensitive and 80% specific in detecting cases of HAND when using a cut-off score of 11 or below. Although the cut-off score of 11.5, with a sensitivity of 83%, seems the most appropriate, the cut-off value of 11 points offers a substantial increase in specificity of 12%, with only a small reduction in sensitivity of 3%. The same applies to the positive predictive value, which increases by 8%. These two facts allow a substantial reduction in false-positive results with a minimal reduction in the amount of subjects detected with cognitive dysfunction. Lastly, the J-Index is also slightly higher in this case, confirming that **a cut-off value of 11 is more useful** than one of 11.5 -or any other- **when using the IHDS for screening for HAND in general.**

When screening for HAD cases only (Table 3.5) **a cut-off value of 10 results in an increase in both sensitivity and specificity** when compared to the general cut-off value of 11. Also, the J-Index indicates that when we focus on this specific group of patients at risk of more marked disease, a cut-off value of 10 is better than 11, achieving a value of up to 0.8. Fig. 4.1 shows the information from both Tables 3.4 and 3.5 in a clearer way.

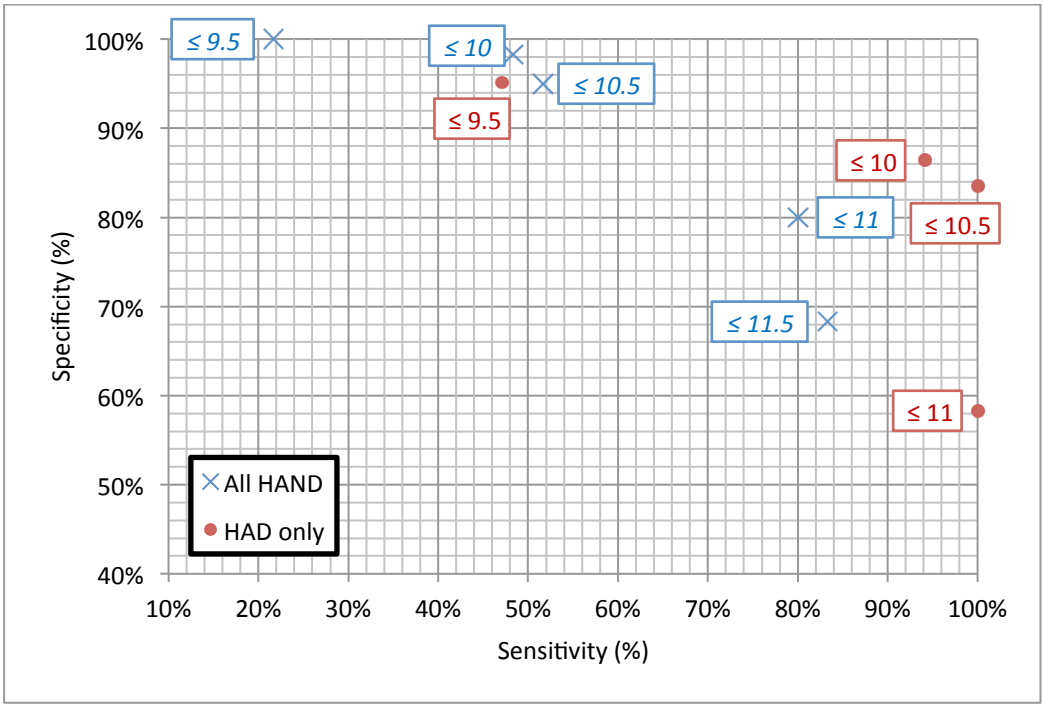

Fig. 4.1 – Sensitivity and specificity of several cut-off values.

In blue and marked with a cross (×), cut-offs for detecting HAND in general (ANI+MND+HAD).

In red and marked with a dot (•), cut-offs for detecting HAD cases only.

Using the reported cut-off points of 11 when screening for HAND in general and 10 when screening for HAD only, the sensitivity of the IHDS in our cohort reaches 80% and 94%, respectively. These values are similar to the ones obtained by Sacktor et al. in 2005 in their studies on US and Ugandan populations [41], as well as in further studies that have used this tool in other populations and countries [71-76].

In 2013, two systematic reviews of over ten studies that had used the IHDS concluded that the sensitivity obtained in those studies was generally low. Zipursky et al. [77] calculated the IHDS to be 62% sensitive for HAND, whereas Haddow et al. [42] calculated it to be 64% sensitive for HAND and 74% for HAD. Moreover, Haddow also pointed out a lack of accuracy when screening for the milder forms of HAND - ANI and MND- due to a low specificity, which he calculated to be 66%. These two papers are the largest and most rigorous meta-analyses of studies using the IHDS that have been carried out to date. Their conclusions differ significantly from those in this study. **These differences are caused by the variety of existing socio-cultural**

frameworks among the evaluated populations and the diversity of countries in which the studies took place, which, in our opinion, justifies the local standardisation and validation of the screening tool for each unique social and cultural context. As Haddow points out, the majority of IHDS studies have been conducted in Sub-Saharan Africa, whereas this study has been conducted in Northern Europe. This implies huge changes in population, as well as educational and therapeutic features. Also, although developed to be cross-national, the IHDS is not free from socio-cultural-linguistic effects: for example, the four-word recall task, which must be modified for different languages. Other sources of variability between the studies reviewed in the meta-analyses and this one may be the studied population − some with advanced immunodeficiency, others with confounding diagnosis: whereas those in this study were almost exclusively male, and the majority of confounding diagnoses were screened out. More importantly, the majority of the reported studies (>80%) in both meta-analyses used a HAND/HAD definition different or prior to the 2007 Frascati criteria. This fact definitely influenced the outcome of the mentioned studies due to differences in the reference standards applied. Furthermore, the lack of a common neuropsychological battery of tests that works as a real gold standard for diagnosing neurocognitive impairment in HIV infected individuals, clearly limits comparing outcomes between study groups. **In our case, the recorded specificity is slightly higher than that reported in previous studies,** with specificities and J-Indexes of 80% and 0.6 when screening for HAND in general and 86% and 0.8 when screening for HAD specifically.

The results of our analyses confirm that the IHDS produces positive results with regards to accuracy as well as ease of use and applicability. Despite not being a substitute for complete neuropsychological testing, the IHDS has been shown to be effective in revealing those patients at higher risk of developing HAND, which allows healthcare providers to refer these patients for neuropsychological evaluation when needed. Therefore, based on the results of our study, **we suggest the following recommendations when using the IHDS in a German-speaking population:**

1. All patients who score 11 or below should be neuropsychologically tested in order to exclude an ongoing HAND.

2. Those who score 10 or below should be evaluated without delay, as this indicates a higher likelihood of being diagnosed with HAD.
3. All patients who score over 11 points and actively express cognitive complaints should also be neuropsychologically tested in order to exclude ongoing HAND. Current major depression or psychiatric disturbance should be ruled out as a cause of the complaints.
4. All those who score over 11 points and do not express any cognitive complaints should be rescreened in six months.

Please note that an 'abnormal' screening result should not be interpreted as a conclusive diagnosis of dementia. The screening result could be influenced by other comorbid conditions, such as low mood, depression or substance use. Also, if advanced impairment is highly suspected, neurocognitive assessment should not be deferred in any case, regardless of the score obtained in the screening procedure.

- When to start screening: the first screening should be performed as soon as possible, ideally in the first six months after being diagnosed with HIV. This allows the clinician to obtain a baseline value of the patient's cognitive function, which can be used as a reference in case of eventual cognitive decline.
- When to rescreen: screening should be continued and re-evaluated periodically even if a patient remains neurocognitively stable over a longer time, as this can show the evolution of the patient's performance allowing for an early intervention if a decline is detected. In general terms, screening should be repeated every six months. Some specific situations may require rescreening more often. In the case of treatment naïve patients, or patients who decided to interrupt or pause their treatment, screening should be repeated every six months. Especially if there is an evidence of a rapid deterioration of the cognitive function, screening should be repeated without delay. Also changes in the cART regimen will require retesting, but this should occur after an adjustment period of six months.

Theoretically, the IHDS could be used for rescreening as well as for monitoring purposes of patients with an already diagnosed HAND. In order for the IHDS to track fluctuations in cognition, it is important to determine the test's repeatability, intra-

subject variation, and learning effects [42]. This study did not address this issue. A literature search provided a study that evaluated the test-retest reliability of the IHDS when performed twice on the same patient within a one-week interval [78]. The study showed a good test-retest correlation between the total score, the finger tapping and psychomotor tasks, however the correlation reduced in the memory recall task. Indeed, this study does not answer the question about a possible learning effect on the four-word task when retested. Nevertheless, a second version of a test for avoiding learning effects when retesting is available for a number of neuropsychological tests. From our point of view, it would be of major interest and utility to have further standardised sets of four words available for re-screening purposes.

The application of the IHDS in a primary care setting has been welcomed and positively evaluated both by patients and healthcare practitioners. The main limitation was the test's inability to discern between HAND subtypes, especially between ANI and MND. Concerning our study, this was of lesser importance, as our aim in this very initial diagnostic stage was to see if the test was able to reveal which individuals were at risk of HAND in order to refer them for neurological evaluation, without the need for further characterising the deficit. Nevertheless, the ability of a screening tool to discern between ANI, MND and HAD remains a key area of discussion and debate in the NeuroAIDS field. **The IHDS, as it is currently designed, does not allow evaluating cognitive decline, which hinders a HAND subclass differentiation.** This could be easily completed in a future version of the screening tool by adding an item evaluating functional decline as a fourth point of evaluation (i.e. short questionnaire or direct questions from the examiner). As an example of the latter, we conducted an analysis that individually crossed the results of the IHDS and the neuropsychological assessment with the DNAA questionnaire in order compare the HAND outcome depending on the neuropsychological tool used. 53% (48/90) had been marked as impaired in both tools; 23% (21/90) as unimpaired in both tools; and 23% (12+9/90) had divergent results between tools. The correlation coefficient between the results obtained in IHDS and neurocognitive assessment when comparing impaired vs. unimpaired was $r = 0.49$ ($p < 0.001$). With a 23% of inaccuracy of the IHDS when used for diagnosing HAND, this analysis shows that the use of this tool as a substitute for the neuropsychological examination is not recommended.

4.2. Commentary on the cohorts' prevalence of HAND

There is a wide divergence in HAND prevalence rates depending on the source consulted. This can be seen in Table 4.1, which shows the observed prevalence of HAND and its subtypes in several cohorts in similar countries. It is worth noting that HAND prevalence rates differ considerably between study groups, and that there is no particular pattern regarding the three diagnostic subtypes, aside from the trend that ANI is more common than MND which itself is more common than HAD. The divergence goes from 69% affected in a wider cohort of people living with HIV in French-speaking Switzerland [47] to 21% in a more specific cohort of urban men who have sex with men (MSM) in the London metropolitan area [79]. **In general, it can be derived that HAND affects about half of the people living with HIV, and that the prevalence of HAND and its subtypes found in our cohort was similar, but not equal, to that reported by other investigators.** Indeed, the available data shows that HAND prevalence remains high regardless of the wide use of antiretrovirals and, specifically for the Berlin cohort, despite the close medical surveillance that these patients get.

Table 4.1. – Prevalence of HAND, its subtypes, and NCI in negative controls in different cohorts from more economically developed countries

Cohort Name	*HAND*	*ANI*	*MND*	*HAD*	*NCI in HIV-*	*Year*	*Reference*
Swiss Cohort	69%	50%	17%	2%	--	2010	Simioni [47]
Aquitaine Cohort, France	59%	21%	31%	7%	--	2013	Bonnet [80]
OHTN Cohort, Canada	58%	34%	11%	13%	--	2013	Rourke [81]*
Sydney, Australia	53%	--	--	--	14%	2014	Cysique [82]
NEU Cohort, Catalonia, Spain	48%	--	--	--	--	2013	Munoz-Moreno [83]
CHARTER Cohort, US	47%	33%	12%	2%	--	2010	Heaton [6]
Berlin	**43%**	**20%**	**17%**	**6%**	**10%**	2016	This study
Duesseldorf, on cART only	42%	28%	10%	4%	--	2014	Arendt [84]*
Duesseldorf, all HIV+	28%	15%	8%	5%	--	2014	Arendt [84]*
CIPHER Cohort, UK	21%	14%	7%	1%	30%	2014	McDonnell [79]

* Unpublished data presented in conferences and available as additional material on p. 71-72

Several reasons explain this fluctuation. Firstly, population differences existing between the different study groups -age, gender, educational level, comorbidities and viral control- play a determinant role in the reported prevalence [85]. For example, the CIPHER Cohort [79] from London consists mostly of highly educated men with both formal and informal education, successfully virologically supressed, and neurocognitively stable, which leads to a low prevalence of HAND as a result of low morbidity in general due to a successful cART. Similarly, age plays a critical role in diagnosing HAND cases. From a recently published study by Fogel et al. [85] comparing cohorts of young versus older HIV-positive people, we learned that there is an increased prevalence of NCI in older HIV-positive individuals, as well as an altered presentation of HAND.

Secondly, the use of standardised norms might not be applicable to populations of a different socio-cultural environment, nor for specific subpopulations of a larger cohort. This was reported by Cysique et al. in a study that showed different HAND prevalence rates when applying US or Australian norms to the same raw scores obtained in a neuropsychological evaluation by a group of patients. These varying prevalence rates were concerning as both cohorts were thought to be educationally and culturally similar [82]. This false assumption resulted in the use of the US standardisation norms in many Western countries, which led to misclassification of patients, thereby altering the proportions of affected individuals and the global prevalence in the cohort. There is an increasing need to develop local normative standards that apply to specific linguistic, social and cultural groups of populations and their subgroups. **This was one of the main goals of this study: the development of a new normative standard for the IHDS with new cut-off values and proceeding recommendations valid for all German-speaking populations.**

Thirdly, the diagnostic algorithm proposed in the Frascati criteria might be too rigid and too dependent on neuropsychological tests that were mainly designed for non-HIV purposes in the pre-cART era and validated in younger cohorts for whom age-related comorbidities were not considered. The Frascati criteria were originally proposed as an algorithm for research settings [18]. The fact is that currently they are widely being used in a clinical context. As Haddow reports in his article, *"The Frascati criteria are relatively detailed, objective, and appropriate for a research*

definition, […] However, current data do not clearly inform clinicians of the natural history or appropriate treatment of these conditions, particularly milder impairment" [42]. The non-existence of other definitions more applicable to a clinical setting limits its interpretation, and makes it hard to conduct an objective approximation of the actual prevalence of the disease in the HIV-positive population. On the one hand, the current definition is too convoluted for all non-neuroAIDS familiarised healthcare providers, due not only to its need for complex understanding of definitions but also as a result of the interpretation of the psychometric part. On the other hand, the definition is too vague, especially in ANI cases, where the diagnosis relies uniquely on numbers –the negative standard deviations-, without any consideration of other important clinical and immunological data.

The significance of ANI has been questioned by some authors, implying that, as it is now defined, it falsely inflates the prevalence rate [79]. Authors such as Gisslén and Price have pointed out that "*the definition of ANI is not stringent, and results in approximately 20% of the population being classified as abnormal. To us [Price, Gisslén & Nilsson] this seems an unacceptable false-positive rate*" [86]. The uncertainly of the significance of ANI has arisen in the NeuroAIDS field since the publication of the Frascati definition. In their article, McDonnell et al. suggest that the actual diagnostic algorithm generates a high false-positive rate, which they refer to as being a statistical artifact of the particular testing procedures and algorithms proposed by the currently accepted definition, and end by pointing out that diagnosing an asymptomatic HAND might be a waste of resources which may also lead to unnecessary worry for patients. This statement could be supported by the fact that 10% (3 participants) of our healthy controls had criteria of ANI after completing cognitive testing. Besides that, using a Gaussian distribution, 15.9% of a population should perform below -1 standard deviation. Therefore, it was suggested that raising the impairment threshold in neuropsychological tests to 1.5 negative SD in order to reduce false-positive rates is more appropriate. In contrast, other newly published studies have added reliable data that supports the clear prognostic significance of a diagnosed ANI. A study by Grant et al. showed that being diagnosed with ANI increased the risk of suffering MND or HAD two to six times. These results would strongly support the prognostic value of an ANI diagnosis, offering opportunities to modify treatments earlier and to delay the disease's progression [87]. Focusing again

on the Berlin cohort, results indicate that almost half (47%) of the HAND diagnosed cases were asymptomatic. A further neuropsychological evaluation of the patients in this cohort, after a time interval, might clarify this point, as it would record any progression − or regression − in their HAND stage.

Finally, the size of the neuropsychological testing battery, which in the case of this study included eleven tests covering eight different ability domains, is relatively bigger than that used by other study groups. This fact increases the likelihood of obtaining a lower score in more than two domains. The Frascati definition restricts the description of the neuropsychological assessment to a minimum amount of domains to be tested and, it adds, "*if possible, with at least two test measures per domain*" [18]. This means that the battery of tests could consist of five tests – or double. The probability of the examinee obtaining -1 SD in more than two cognitive domains is directly proportional to the number of completed tests; therefore the chances of being diagnosed with ANI increase with the number of tests within the battery. Moreover, the definition does not refer to single tests that evaluate two ability domains. It is unclear if both domains should be marked as affected, if the examinee gets to fail a test that evaluates two ability domains. In this case, it would only be needed to fail one test to get an ANI diagnosis. It is clear that the size of the battery of tests matters − but also the kind of tests selected. At present, there is no consensus about what tests should be part of a common neuropsychological battery of tests for detecting HAND. The Mind Exchange Working Group published some recommendations on comprehensive neuropsychological testing, and the development of a common and universal battery has been discussed, but without consensus [28]. **From this study it can be concluded that certain tests correlate better with the diagnosis of HAND than others, especially the TMT Part A and B tests, the d2 concentration test and the Digit Span test.** Testing attention/working memory and information processing speed has been described as particularly useful in detecting neurocognitive impairment in people living with HIV [88]. **From the author's point of view, these tests should be part of any neuropsychological battery of tests for detecting HAND, given their high predictive power as well as easy performance and interpretation.** Further agreement and consensus on a more precise definition of the battery of tests (e.g. number of tests per domain, recommendation of which tests

should preferably be used) could homogenise the evaluation frameworks between study groups and could prevent the fluctuations in reported prevalence.

4.3. Commentary on potential risk factors

This study reveals a large proportion of subjective cognitive complaints as well as neuropsychological deficits despite the wide use of antiretrovirals with an assumed appropriate CNS penetration index. As mentioned in Table 3.1, 89% of participants were on treatment and the mean CPE score was found to be higher than seven for all study groups. A priori, this appears to show a negative effect of cART over cognition, or at least no beneficial effect. This fact may have its own explanation, as patients receiving cART were commonly those who had been living with the virus for longer, allowing more episodes of immune suppression, which could have ended in neurodegeneration. These circumstances have changed in recent years, with the tendency to start antiretroviral treatment as soon as possible after diagnosis, regardless of the immune status of the patient. This has been recently backed by the conclusions of a major randomised trial, the START Study [89], which found more benefits in starting an antiretroviral treatment at the moment of being diagnosed rather than waiting for a $CD4^+$ cell count decline under 350 cell/μL. In contrast to this approach, a recent article signed by Underwood, Robertson and Winston widely revises the topic of antiretroviral neurotoxicity. In their paper, they point out that *"to date, there has been little focus on potential neurotoxic effects of antiretrovirals agents, despite this being a potentially modifiable risk factor"* [90]. The article reviews several studies that have evaluated the neurotoxic effect of different antiretroviral agents on neuronal cell cultures, as well as major cohort studies revealing a reduction of CNS-related symptomatology after therapy switch or interruption. This could correlate to this study's findings of less reported subjective cognitive complaints in patients who are currently not being treated, as showed in Fig 3.3. The authors also mention that the high prevalence of light to mild HIV-associated neurocognitive impairment is most probably due to the antiretroviral-induced dysfunction of the neuronal mitochondria and the neurone's oxidative metabolism. This reduction in the available energy would cause neuronal death, which would concurrently exacerbate a proinflammatory environment that would increase the activation of microglial cells and macrophages in the CNS compartment. Clinical

trials to further study the neurotoxic effects of antiretroviral agents are likely to increase in the future. These trials should find a drug combination that correctly supresses the viral replication while having the minimum effect on the CNS cells.

When asked if they were currently experiencing cognitive complaints, 35.8% of the study population reported experiencing some in the last three months. This proportion rose to 90% in the 'poor performance' group. **This shows which population to focus on more: those actively declaring cognitive complaints.** More work should be performed on this group of patients in order to better understand the high level of complaints and also to discard possible viral escape situations. Interestingly, the 'high performance' study group reported more cognitive complaints than the HIV-negative control group. By contrast, this did not translate in a worse outcome in the neuropsychological evaluation, where both groups obtained similar mean scores in the individual tests of the battery, showing no significant differences. **This divergence partially opposes our initial thoughts of these two groups having a comparable cognitive profile.**

The wider analyses of the data from the Berlin cohort brought up several other key factors, which potentially could lead to an early detection of a disorder. Education, measured as years attending a teaching institution, proved to be an important predictor of HAND diagnosis. The fewer the years spent in education, the greater the risk of developing the disease, especially in its more severe forms. Age also appeared to be a significant risk factor in developing HAND [31]. Both formal education and age have been reported to have an influence in the outcome of neuropsychological tests. Even after applying demographic corrections for these two factors, education and age showed to have some degree of correlation with HAND. These finding have also been reported by other study groups in the past [30, 31]. By contrast, having a non-German linguistic background did not show any specific effect on the neuropsychological outcome. Even if the statistical significance of a variable with such wide standard deviations might be questionable, in this cohort, participants with a lower $CD4^+$ nadir had higher HAND incidence. $CD4^+$ nadir has been considered to have an association with cognitive impairment in HIV-infected individuals by many authors [91-93]. A state of extreme immune suppression with low $CD4^+$ cell counts is likely to produce irreversible neural injury [91]. Combined with the certainty that ongoing replication

in the CNS causes cognitive difficulties despite controlled systemic viral suppression [19], these two arguments support an early start of antiretroviral treatment in all HIV-positive patients to reduce the risk of HAND.

In a similar study to this one, performed in 2012 in Spain, evaluating cognitive complaints in HIV-infected people using a self-reported questionnaire, investigators found that almost half of the sample (49.8%) experienced some, with memory and attention the areas most commonly perceived as affected. The complaints correlated with a longer duration of the HIV infection, a lower $CD4^+$ cell count, undetectable viral load and poor quality of life. They also generated a profile of the person most at risk of experiencing cognitive complaints: these were older people living on their own, which had a lower level of education and had suffered from depression or anxiety [94].

The previously mentioned article from 2015 by Fogel et al. [85], comparing two groups of HIV-positive people (young [32-50, mean 43.8] vs. older [55-73, mean 61.1]) analysing the influence of several risk factors in the HAND diagnosis increased the available information about this subject. Thanks to a stepwise regression model comparing HAND diagnosis and possible associated variables that are routinely collected in primary care settings, this group of investigators found out which risk factors were useful variables for predicting HAND, depending on the age group of the patient. In the younger cohort, they found cocaine and methamphetamine abuse, lower circulating haemoglobin, and, similar to the findings of our study, an older age and time since being tested positive, to be related to a higher incidence of HAND. In this study, substance abuse was listed as an exclusion criterion due to its known mind-altering proprieties and its effect on the neuropsychological outcome. In the older population, the variable with the highest correlation was years of known infection, followed by depression – which we excluded as a confounder − and hyperlipidaemia. This last finding suggests the existence of a cerebrovascular component in the development of this condition and could also indicate an increased inflammation level in the older cohort, as other research groups lead by Becker [95], Foley [96] and Cysique [97] have already reported. Their evidence, which is confirmed by the data in this study, indicates the significance of **expressing cognitive complaints, lower educational level, older age, a longer duration of the HIV infection and a lower**

$CD4^+$ nadir, and suggests that these are true risk factors to be taken into account for future screening tools, due to their predictive value. In contrast, the low number of patient receiving efavirenz or with hepatitis C coinfection did not indicate a direct relation between these factors and developing HAND. These points should be readdressed in future studies more focused on one or both of these aspects.

4.4. Further comments on the methods applied

Comments on the IHDS and the neuropsychological tests have been widely discussed at the beginning of this chapter. As already reported in the prevalence section, this study showed that some neuropsychological tests (TMT A & B; d2; Digit Span) had a better correlation with HAND diagnosis than others, and should therefore be preferentially used. Other tests like the Rey Auditory Verbal Learning Test, the Rey Visual Design Learning Test and the Rey Osterrieth Complex Figure require a longer time to complete. In order to streamline neuropsychological evaluations, tests that take longer than five minutes to carry out should, wherever possible, be replaced by others of shorter duration evaluating the same domain. Also some of the current paper based tests could be transferred to an electronic format. The use of computers and other devices such as smartphones and tablets could simplify the neuropsychological assessment as well as reinforce the examinees' motivation since, when carried out electronically, the tests are more like a videogame than an exam. Clear recommendations on which tests should preferentially be part of a neuropsychological battery of tests should be given − an international consensus on a "HAND testing battery of tests" working as a real, common gold standard should be a future goal in the NeuroAIDS field.

Some groups have tried to develop an "imperfect gold standard" or "silver standard", halfway between a short screening test and a long complete neuropsychological assessment by selecting specific tests in a medium sized battery. The NEU Screen combined three paper-based tests (TMT A for attention/working memory; TMT B for executive function; COWA for verbal fluency), which took less than 10 minutes to perform and obtained a sensitivity of 75% and a specificity of 82% [83]. Similarly, another group used four tests (Stroop; Hopkins Verbal Learning Test; Paced Auditory Serial Addition Test; Action Fluency), completed in 18 minutes and obtaining a

sensitivity of 86% and a specificity of 87%. This last paper also points out the usefulness of tests evaluating verbal learning, attention/working memory and speed of information processing [88]. The conclusions of the latter two study groups are in accordance with the results of this study, which shows the highest correlation between HAND diagnosis and the scores obtained in the TMT A and B as well as the d2 and Digit Span tests, which evaluate processing speed, executive functioning and attention/working memory.

Particularly remarkable was the use of the self-reported DNAA questionnaire. This tool proved to be useful in detecting subjective cognitive complaints. Nevertheless, it could be improved by simplifying the wording of several questions - some included a double negative, which induced doubt in several participants. This questionnaire also asks about other neurological conditions related to HIV, such as neuropathic pain and the use of older antiretrovirals with well-known neurotoxicity. As the focus of this study was on the cognitive aspects, the removal of these questions could be considered if the aim is to save time.

This study has several limitations: this is a single centre study, with a relatively small sample size and a limited gender profile -in our case almost exclusively men who have sex with men recruited at a single health centre-. A single physician trained in neuropsychology – the author − was in charge of performing all 120 neuropsychological evaluations, which slowed down the process of data collection. Additionally, there are individual factors of the participants that work as diagnostic confounders – such as past episodes of depression, long-term unemployment and the use of alcohol and substances in the past. As already mentioned, a learning effect on the four-word task of the IHDS may appear when re-testing. This is a known event in neuropsychological testing that can be easily solved by designing different versions of the same task, which must be similarly empirically validated prior to its clinical use. If this task is to be utilised in a longitudinal context, future studies are required to clearly understand the role of practice effects, test-retest reliability, and regression to the mean on test scores in this local population. Seventy percent of the screened population obtained an almost perfect IHDS score. This suggests a ceiling effect that could question the utility of the test. A possible explanation could be the educational makeup of the sample, with a high proportion of university-educated participants.

However, the use of the IHDS has managed to refer patients without apparent clinical abnormalities to neuropsychological assessment, which confirmed an asymptomatic neurocognitive disorder. In addition, its use has brought awareness of a condition that patients and primary care doctors were previously not familiarised with, as they now openly speak about it. We find these achievements to be of major importance. Cognitive complaints were evaluated by a single, self-reporting questionnaire. All answers were given as dichotomic, which could have limited the information obtained, although its use is widely spread in research. Also, when applied to a group of patients with advanced impairment, self-reported questionnaires may lack the ability to provide an accurate response, as these patients may be unaware of their own decline. Their answers can mask their actual symptoms, and can result in a misclassification of that patient as asymptomatic. Finally, the size of our neuropsychological battery of tests was relatively larger than that used by other study groups, increasing the likelihood of obtaining a lower score in two or more domains.

4.5. Future screening options

At present, brief neurocognitive screening tools, such as the one evaluated in this study, are being used to detect HAND in primary care settings all around the world. Because of its closeness to patients, it is precisely in this setting where clinical, virological, demographic, behavioural and psychosocial data can be collected most easily.

Ideally, HAND screening should evolve to a model of integrative information screening, using tools for collecting and analysing data and statistical methods capable of integrating complex and multifactorial features in order to predict neurocognitive impairment. This data has been currently ignored in the majority of screening algorithms, which are based on neuropsychological testing. These new screening procedures should analyse data coming from different sources and integrate it in order to predict the probability of suffering the condition. Potentially useful information includes:

- Immunological: historical $CD4^+$ cell counts, $CD4^+$ nadir, estimated duration of infection
- Demographic: age, educational level

- Reported cognitive complaints
- Comorbidities: depression, substance use, past CNS or HIV related diseases
- Therapy related issues: neurotoxicity of long-term use of antiretrovirals, its CPE
- Other co-medication in use
- Neuroimaging findings (where available)
- Biomarkers and neurodegeneration indicators

Authors such as Becker and Cysique have made several attempts in this direction, with variable success [35, 97, 98]. Much of this data is already available and contained in "the cloud" that forms our electronic health records, a system of collecting and storing information that has expanded its use in the last decade and will continue to do so. This large amount of data has the potential to be "mined" for information.

These future screening options should consider any upcoming redefinition of the Frascati diagnostic criteria. In a hypothetical new adaptation of the HAND definition, neuropsychological assessment should continue to be one of the components of the diagnosis, but probably not as critical and central as it is today. As mentioned previously, neuropsychological testing should be complemented with further information. A common, standardised neuropsychological battery of tests should be consensually defined and internationally accepted. In order to reduce false-positive results, the deficit threshold will have to be raised to a z-score of -1.5 SD per evaluated test to define an abnormal domain. To save time, the analysis should be limited to 3 to 5 cognitive domains [99]. Some work on this has already been carried out, as reported previously and referred to under the name of silver standards, giving rise to medium-length neuropsychological batteries of tests with durations of less than 20 minutes and sensitivities and specificities of around 80 to 85%. The IHDS is useful and could therefore be one of the tests contained, as a whole or some parts of it, in this short versioned battery of tests with screening purposes.

4.6. Conclusions

This study proves that HAND are still widely present among people living with HIV. Even when having the widest options of antiretroviral medication and

treatments available, the prevalence of HAND in the Berlin cohort remained high: 43%, or 20% ANI, 17% MND and 6% HAD.

Cognition was worse in HIV-positive than in HIV-negative participants. In general terms, HIV-positive participants referred more cognitive complaints and obtained lower scores in the neuropsychological evaluation than HIV-negative controls. More specifically, the 'high performance' HIV-positive study group reported more cognitive complaints than the HIV-negative control group, but this did not translate in a worse outcome in the neuropsychological evaluation. **This divergence partially opposes our initial thoughts of these two groups having a comparable cognitive profile.**

This study has developed a new normative standard for the IHDS with new cut-off values and proceeding recommendations valid for all German-speaking populations. The optimal cut-off on the IHDS for detecting HAND cases in general was set at 11 and achieved both a sensitivity and a specificity of 80%. When specifically screening for HAD, a cut-off value of 10 offered an increase in both sensitivity (94%) and specificity (86%). The Youden Index for diagnostic accuracy was 0.6 and 0.8, respectively.

The IHDS has been proven to be an inexpensive, rapid and easy to administer screening tool for HAND. It is effective in discerning between patients with possible neurocognitive impairment and those with normal neurocognitive function.

Screening for HAND is an interesting approach in primary care. A regular screening can detect early impairment and defines a cognitive trend even before the patient starts expressing subjective complaints. Screening for HAND should be an essential part of any new HIV diagnosis and become part of regular medical check-ups in chronically infected patients in order to improve the general prognosis of the condition.

Expression of cognitive complaints, lower educational level, older age, a longer duration of the HIV infection and a lower $CD4^+$ nadir were the factors that correlated best with a HAND diagnosis. Due to their predictive value, these factors

should be taken into account when designing future screening methods. The small sample size did not allow yielding the significance of other factors such as the use of antiretrovirals or a hepatitis C coinfection. Nevertheless, there is increasing evidence suggesting potential neurotoxicity of several antiretrovirals. In the upcoming years, antiretroviral agents should be improved in order to reduce any long term neurotoxic effect, but therapy should continue being started as early as possible in order to minimise HIV-induced neural injury. Finally, further studies to specifically evaluate the relationship between hepatitis C coinfection and HAND should be readdressed in the future.

From this study it can be concluded that certain tests correlate better with the diagnosis of HAND than others. Tests such as the TMT Part A and B, the Digit Span and the d2 concentration test should be part of any new consensual neuropsychological battery of tests for detecting HAND, given their highly predictive power, as well as ease of use and interpretation.

Looking forward. Future screening algorithms should complement the neuropsychological tasks with a wide range of clinical, immunological, demographic, therapeutic, behavioural and psychosocial variables. Much of this data is already available in electronic health records and has the potential to be used for clinical and research purposes.

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ADDITIONAL MATERIAL

Questionnaire of the DNAA – Page 1

SNAS – Short Neuro-AIDS Screening - German NeuroAIDS Study Group

DNAA Deutsche Neuro-AIDS Arbeitsgemeinschaft e.V.,
http://www.dnaa.de

NeuroScreening

für Neurokognitive Defizite in HIV+ Patienten

Patientennummer:	*Geschlecht:* ☐*M* ☐*V* *Alter:*
Können Sie seit mehr als 3 Monaten nicht mehr konzentriert den gewohnten Arbeiten und Freizeit-Tätigkeiten nachgehen? ☐ *Ja* ☐ *Nein*	*Fällt Ihnen mehrmals am Tag ein Gegenstand aus der Hand?* ☐ *Ja* ☐ *Nein*
Müssen Sie die Seiten eines Buches oder einer Zeitung mehrfach lesen, um den Inhalt zu behalten? ☐ *Ja* ☐ *Nein*	*Sind Sie seit mehr als 3 Monaten depressiv gestimmt, ohne dass große Veränderungen in Ihrem Leben aufgetreten sind?* ☐ *Ja* ☐ *Nein*
Hat sich Ihr Schriftbild verändert? ☐ *Ja* ☐ *Nein*	*Sind Sie tagsüber ständig müde, obwohl Sie nachts schlafen?* ☐ *Ja* ☐ *Nein*
Können Sie kleine Schrauben nicht mehr andrehen, keine Knöpfe mehr annähen oder sind Sie am Computer langsamer geworden? ☐ *Ja* ☐ *Nein*	*Haben Sie mehr als 3 Monate andauernde Ein- und/oder Durchschlafstörungen?* ☐ *Ja* ☐ *Nein*

	Ja	*Nein*
Spricht Ihr persönliches Umfeld Sie darauf an, dass Sie sich verändert haben?		
Waren Sie in den letzten 12 Monaten mehrfach krankgeschrieben, ohne dass eine internistische/allgemeinmedizinische Erkrankung zugrunde lag (allgemeiner Erschöpfung)?		
Sind Sie älter als 65 Jahre?		
Sind Sie bereits seit dem Kindes-/Jugendalter mit HIV infiziert?		
Befinden Sie sich zur Zeit in einer Therapiepause?		
Haben Sie eine antiretrovirale Therapie bei einer geringen CD4-Zellzahl (<250Zellen/ml) begonnen?		
Gibt es eine nachweisbare Viruslast trotz der Therapie?		
Verspüren Sie ungewöhnliche Kribbel-/Wärme-/Kältegefühle, Schmerzen oder Taubheit in den Händen und Füßen?		
Stolpern Sie häufig?		
Bemerken Sie einen Rückgang der Muskulatur, nicht gut heilende Wunden oder Verfärbungen der Haut an den Füßen und Unterschenkeln?		
Haben Sie Potenz- bzw. Libidostörungen?		
Bemerken Sie Störungen beim Wasserlassen?		
Haben Sie Videx, Zerit oder Tuberkulosemittel in den letzten 12 Monaten genommen?		
Leiden Sie unter Diabetes mellitus (Zuckerkrankheit)?		

HCV/HBV Serologien	*Vorerkrankungen*	*Alkoholkonsum*	*Konsum tox. Substanzen*

Note: The design and content have been adapted to the needs of our study.

Questionnaire of the DNAA – Page 2

SNAS – Short Neuro-AIDS Screening - German NeuroAIDS Study Group

DNAA Deutsche Neuro-AIDS Arbeitsgemeinschaft e.V.,
http://www.dnaa.de

Behandler Teil

HIV ED:	*Infektionszeitpunkt:*

Aktuelle ART: ☐

Kommentare
Konzentration
Gedächtnis
Feinmotorik
Stimmung
Schlaf
PNP

International HIV Dementia Scale – IHDS		*Laborwerte*	
MS		*Viruslast-PCR*	
PMS		*T-Helferzellen abs*	
MR		*T-Helferzellen rel*	
Punktzahl	/12	*Ratio CD4/CD8*	
☐*Unauffällig*		*Viruslast Zenit*	
☐*Grenzwertig*		*T-Helferzellen Nadir*	
☐*Auffällig, eine Weitertestung wird empfohlen.*		*TPPA / VDRL*	

Note: The design and content have been adapted to the needs of our study.

Unpublished data presented at conferences and referred to in this work

Rourke SB. *Neurocognitive screening and behavioural interventions for HIV-Associated Neurocognitive Disorders (HAND)*, in *International Forum on HIV and Rehabilitation Research,* 2013: Toronto. Slide 15.

Availabe on-line on the 30th October 2015 at:

http://www.hivandrehab.ca/EN/AGM2013/documents/S_Rourke-CUHRRCPresentationJune132013.pdf

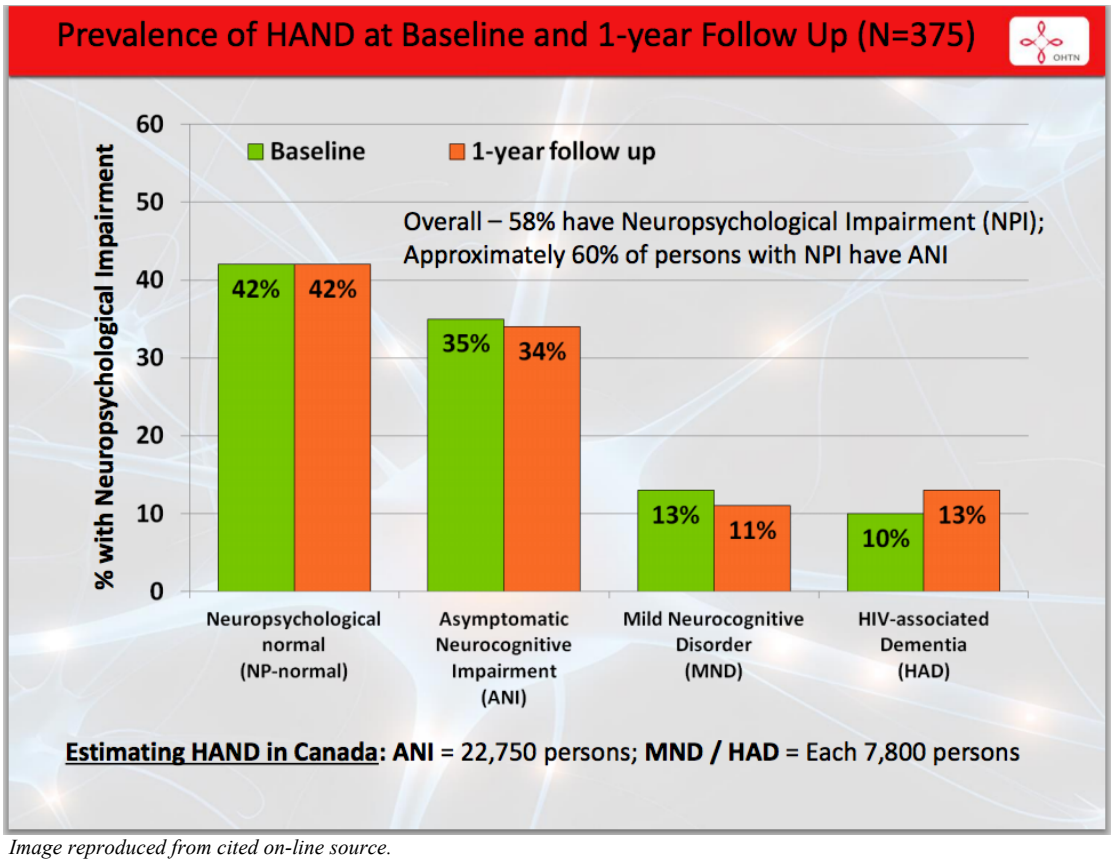
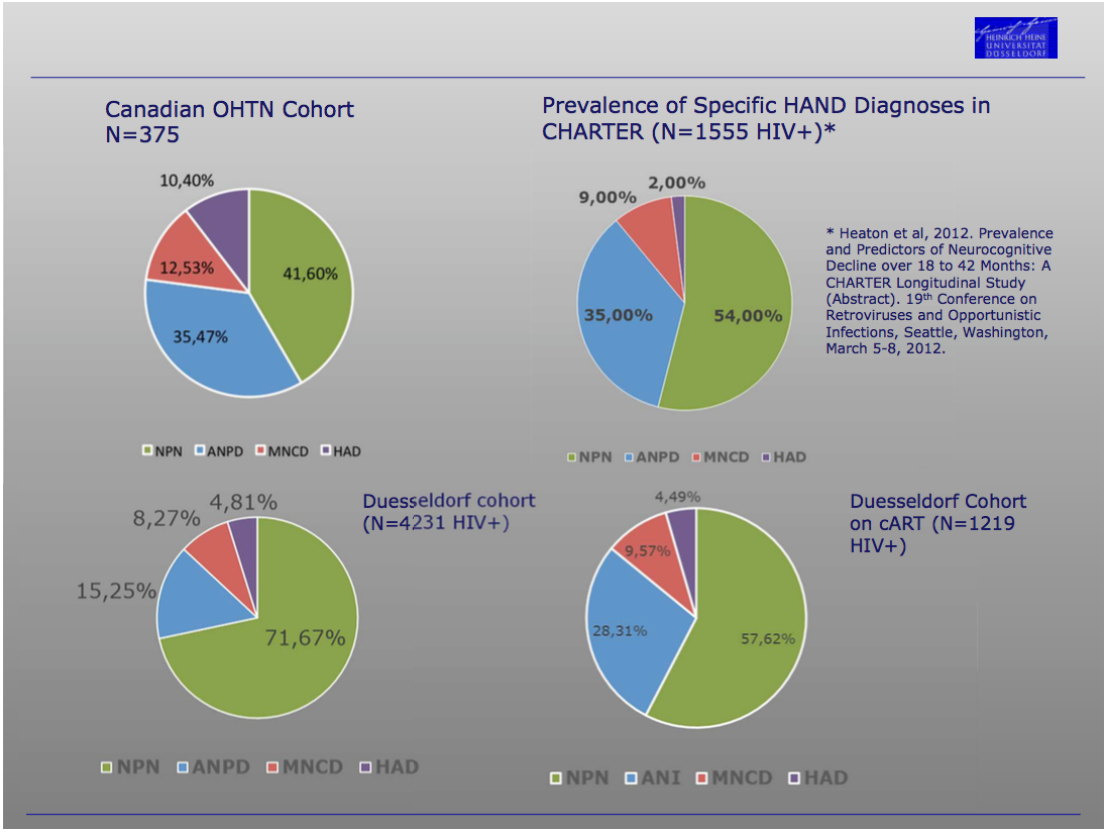


Image reproduced from cited on-line source.

Unpublished data presented at conferences and referred to in this work

Arendt G, Orhan E, Nolting T. *Clinical Progression of Neurological Disease in Well-Treated Patients*, in *North European Workshop HIV Infection in the CNS,* 2014: Berlin. Slide 24.



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AFFIDAVIT

I, Victor Marin-Webb certify under penalty of perjury by my own signature that I have submitted the thesis on the topic:

Screening for HAND:
Validation of the International HIV Dementia Scale as a screening tool for HIV-Associated Neurocognitive Disorders in a German-speaking population

I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (see above) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

“Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.”

“Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.”

LIST OF PUBLICATIONS

Victor Marin-Webb had the following share in the following publications:

Scientific articles:

1. Marin-Webb V, Jessen H, Kopp U, Jessen AB, Hahn K. (2016) *Validation of the International HIV Dementia Scale as a Screening Tool for HIV Associated Neurocognitive Disorders in a German Speaking HIV Outpatient Clinic.* PLoS ONE 11(12): e0168225. 2016. doi:10.1371/journal.pone.0168225

   V. Marin-Webb contributed to the idea, concept and design of the study. He was responsible for the development of the study, which he carried out independently. This included: recruitment of the candidates, performing screening tests and neuropsychological evaluations, reviewing literature, and collecting, analysing and interpreting data. He was responsible for the critical discussion of the results, and for the writing and submitting of the manuscript.

Abstracts, posters and presentations at congresses:

2. Marin-Webb V. *Screening Methoden auf HIV-assoziierte neurocognitive Defizite.* 22. Workshop der Deutsche Arbeitsgemeinschaft niedergelassener Ärzte in der Versorgung HIV-Infizierter e.V. (DAGNÄ). Köln, 14.09.2012, Symposium III. Oral presentation.

3. Marin-Webb V, Jessen H, Hahn K. *HAND Screening in einer HIV-Schwerpunktpraxis.* 6. Deutsch-Österreichischer AIDS-Kongress. Innsbruck, 13.06.2013, Abstract 231, Poster 34. Poster and oral presentation.

4. Marin-Webb V, Ruzicic S, Jessen H. *New Single Tablet Regimens with Integrase Inhibitor – From the clinical trials to its practical use.* 31st Annual Meeting of the Nordic Society of Clinical Microbiology and Infectious Diseases. Bergen, 27.09.2014, Session 6.1. Oral presentation.

   The abstracts, posters and presentations were written, submitted and presented independently.

Signature, date and stamp of the supervising University teacher	Signature of the doctoral candidate
PD Dr. med. Katrin Hahn	Victor Marin-Webb

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Finally, I would like to express my gratitude to the reviewers for their careful consideration of my thesis.