University of Alberta

Decision Making Under Risk in Patients with HIV

by

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Dedication

For my Grandparents:

Simon Theodore Compton
Hilda Elizabeth Tomlinson

For the things you went without; battles you fought; and love and lives you filled.
You remind us to keep our heads down but chins up.

Abstract

Individuals with human immunodeficiency virus (HIV) develop neurocognitive impairments, more frequently as the systemic disease progresses to AIDS. Among HIV-infected persons receiving antiretroviral therapy, executive dysfunctions are very commonly impaired. The present study examined HIV-infected patients' propensity for risky decision making using the Game of Dice Task (GDT), known to covary with executive dysfunctions. Although other tasks and types of decision making have been reported to be impaired in HIV patients, previous study cohorts were complicated by concurrent substance abuse and other comorbidities. Here we used a relatively comorbidity-free population. HIV-infected patients (N=20) were impaired in the GDT, compared to matched healthy controls (N=20). The HIV-infected group also showed an erratic decision strategy across the task. GDT performance was related to measures of executive functioning. Erratic GDT choices were related to current CD4+ T-cell levels. This study provides the first evidence for impaired risky decision making in an HIV-infected population.

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List of Abbreviations Used

AAN	American Academy of Neurology
ACTG	AIDS Clinical Trials Group
AIDS	Acquired immunodeficiency syndrome
ALLRT	AIDS Clinical Trials Group Longitudinal Linked Randomized Trials
ALLRT	Adult AIDS Clinical Trials Group Longitudinal Linked Randomized Trials
ANI	asymptomatic neurocognitive impairment
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	Antiretroviral drug
BBB	blood brain barrier
BOLD	blood-oxygen-level-dependent
cART	combination antiretroviral therapy
CGT	Cambridge Gambling Task
CHARTER	CNS HIV Anti-Retroviral Therapy Effects Research
COWAT	Controlled Oral Word Association Test
CPE	CNS penetration-effectiveness
CSF	cerebrospinal fluid
df	degrees of freedom
D-KEFS	Delis-Kaplan Executive Function System
DOSPERT	Domain-Specific Risk-Taking Scale
DSP	distal sensory neuropathy
fMRI	functional magnetic resonance imaging
GDT	Game of Dice Task
HAART	highly active antiretroviral therapy
HAD	HIV-associated dementia
HADS	Hospital Anxiety And Depression Scale
HAND	HIV-associated neurocognitive disorders
HCSUS	HIV Cost and Services Utilization Study
HCV	hepatitis C virus
HDS	HIV Dementia Scale
HIV	human immunodeficiency virus
IGT	Iowa Gambling Task
IHDS	International HIV Dementia Scale
IQ	intelligence quotient
MCMD	minor cognitive-motor disorder
M	mean
Md	median
MMSE	mini–mental state examination
MND	mild neurocognitive disorder
MoCA	Montreal Cognitive Assessment

MOS-HIV	Medical Outcomes Study – HIV Health Survey
MSK	Memorial Sloan-Kettering
N	number
NIMH	National Institute of Mental Health
PASAT	Paced Auditory Serial Addition Test
PFC	prefrontal cortex
Rg	range
ROCF	Rey-Osterrieth Complex Figure Test
RTI	reverse-transcriptase inhibitor
SAC	Southern Alberta Clinic
SD	standard deviation
SDMT	Symbol Digit Modalities Test
TMT	Trail Making Task
VSRT	Verbal Selective Reminding Task
WCST	Wisconsin Card Sort Task
WHO	World Health Organization

1. INTRODUCTION

The human immunodeficiency virus (HIV) took the world by surprise just over 30 years ago. Intensively studied, the prognosis for individuals infected with HIV today is very different than in the 1980s. Cognitive impairment or *HIV-associated neurocognitive disorders* (HAND) has become increasingly important in the face of long-term management of this chronic disease. One of the less explored cognitive functions in HIV is decision making, the focus of the current thesis. Decision making is a complex cognitive-emotional function of high relevance to everyday life. Few studies have examined decision making in comorbid HIV and substance abusing populations (see section 1.3). None of these studies employed the Game of Dice Task, the test used here to assess decision making under explicit risk in a non-substance abusing HIV patient group. The introduction of this thesis provides an overview on HIV, forms of decision making and their assessment, and reviews existing studies of decision making in HIV.

1.1. Human immunodeficiency virus (HIV)

Considered a pandemic by the World Health Organization (WHO), there are currently over 34 million people worldwide with HIV type 1 (HIV-1). With 1.4 million of such cases in North America, Sub-Saharan Africa accounts for the majority of cases world-wide (UNAIDS, 2011). With the treatment options available today, HIV is no longer viewed as an imminent death sentence but as a chronic illness needing life-sustaining therapies. As with many other chronic

illnesses, prolonged life expectancy can also mean greater likelihood for age-related and other secondary health concerns to arise, including cognitive problems (Wright, Woo, Barclay, & Hinkin, 2009). Discussed here is the influence of HIV on the central nervous system (CNS), the assessment and nature of neurocognitive impairment in HIV, as well as clinical/biological determinants and correlates of HIV neurocognitive impairment.

1.1.1. Neuropathogenesis of HIV

During the period of seroconversion, the HIV virus invades areas of the body known as sanctuary sites; sites include the lymph nodes, skin, gastrointestinal cells, reticuloendothelial system, bone marrow and the brain (Brew & Letendre, 2009). The virus is able to cross the blood brain barrier (BBB) into the brain via a Trojan Horse mechanism; hidden inside a BBB permeable cell (usually a macrophage and/or monocyte) it crosses the barrier undetected (Hult, Chana, Masliah, & Everall, 2008). Once inside the brain, the virus primarily infects microglia (macrophages) and perivascular astrocytes. Through infection of the microglia, the release of neurotoxic agents leads to deterioration of the BBB. While HIV does not directly infect neurons, neurotoxic effects lead to neuronal death as the infection progresses. Microglial nodules, multinucleated giant cells, and gliosis are commonly found in the brains of seropositive individuals, as is diffuse myelin pallor.

Diffuse damage is evident as white matter pallor and synapto-dendritic loss (Power, Boisse, Rourke, & Gill, 2009). Deep gray matter in the basal ganglia (e.g., the caudate nucleus) and white matter such as in the corpus callosum are

particularly affected by HIV (Ances & Ellis, 2007; Power, et al., 2009; Tate, et al., 2009). In addition to caudate/basal-ganglia regions of HIV-associated brain damage, newer studies point to damage in further subcortical and limbic structures, including the hippocampus, as well as to cortical damage, including but not limited to frontal and temporal gray and white matter (Ances et al, 2011; Anthony & Bell, 2009; Moore, et al., 2006).

1.1.2. Neurocognitive Impairment in HIV-infection

Neurocognitive impairment in the HIV population can present in numerous areas of functioning, either directly or indirectly as a result of infection. It is important to attempt differentiation between pre-morbid, disease-related or treatment-related aspects of neurocognitive impairment, although this can be difficult (McCombe, et al., 2009). Although patients in later stages of HIV-infection (during AIDS) tend to be more impaired cognitively, deficits can be found in very early stages of infection as well (e.g., <1 year; Moore et al., 2011).Robertson et al. (2007) examined a group of 1,160 seropositive individuals participating in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) who were initiating or changing treatments. A very brief neuropsychological assessment, comprised of Trail Making Test A and B and the WAIS-R Digit Symbol Test, was used to assess cognitive functioning. At initial assessment, 39% were reported to have mild neurocognitive impairment and 26% had mild to moderate impairment. Twenty-two percent of individuals impaired at baseline remained impaired on follow-up testing 48 weeks post-baseline and 21% of individuals reported to be unimpaired were subsequently

mildly impaired at follow-up. This study highlights the importance of following initially unimpaired study participants, and suggests the possibility of treatment-*induced* neurocognitive changes. (see section 1.1.5.B). However, it should be emphasized that neuropsychological testing was very restricted (only Trails A/B, SDMT) and potential practice effects in this battery were not controlled.

Systems for categorizing the severity of impairment of cognitive impairment have evolved over time. Initially, just the classification of HIV-dementia existed for the most severe cases of neurocognitive impairment. Over time, classification systems to differentiate better between degrees of the severity of cognitive problems were developed.

To detect less severe or earlier stages of cognitive deficits, the Memorial Sloan Kettering (MSK) rating scale was established in 1988. The MSK contains a grading of impairment that ranges from minor cognitive disturbance to incapacitating disorders (Price & Brew, 1988). As the MSK incorporates neurological deficits related to spinal cord damage (myelopathy) and focuses on ambulation, it does not separate well between cognitive/behavioural impairments caused by the involvement of the brain versus those caused by myelopathy. In 1991, the American Academy of Neurology (AAN) redesigned criteria for levels of neurocognitive impairment in HIV (Janssen, Cornblath, & Epstein, 1991). The AAN criteria differentiated minor cognitive motor disorder (MCMD) from HIV-associated dementia (HAD). The MCMD category was reserved for milder forms of motor and/or cognitive dysfunctions than frank dementia.

Present guidelines for classification of HIV-associated neurocognitive disorders (HAND) were established in 2007 by the Frascati working group. The "Frascati criteria" emphasize that the essential feature of HAND is cognitive (not motor) disturbance and also take into consideration the influence of HIV infection on activities of daily living. The Frascati criteria require multiple neurocognitive domains to be assessed including motor skills, speed of information processing, sensory-perceptual, verbal/language, attention/working memory, learning/recall and abstraction/executive functioning (Antinori, et al., 2007). Three levels of impairment can be determined: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) (Antinori, et al., 2007); see Figure 1.1 for a schematic on the Frascati classification criteria and (for a full description see Appendix, Table A.1).

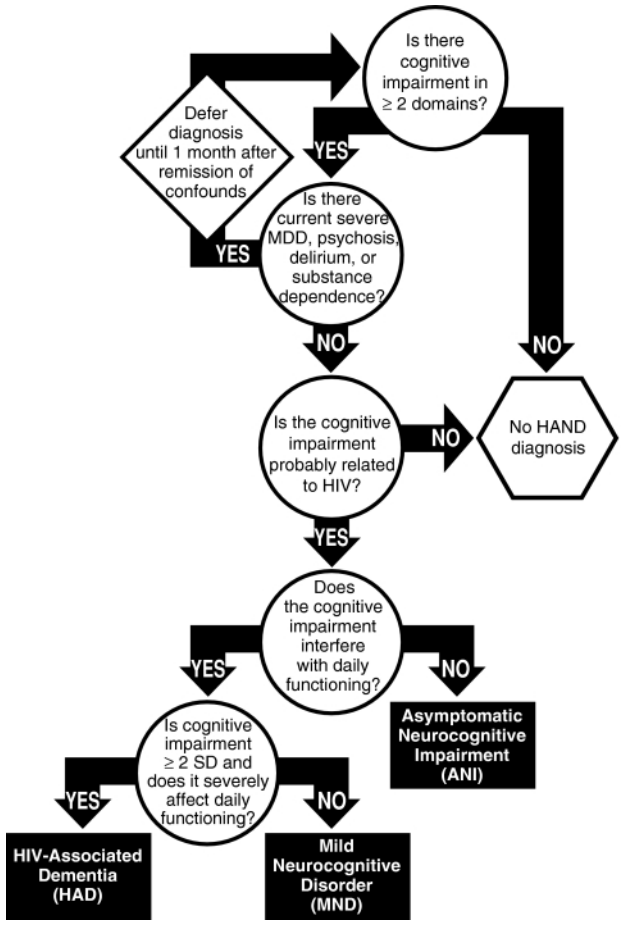

Figure 1.1. Schematic illustrating the diagnosis of HAND category according to the 'Frascati' criteria from Woods, Moore, Weber, and Grant, (2009).

Interestingly, a relatively large proportion of patients classify as ANI according to the Frascati criteria. For example, 33% of patients in the 2010 multi-centre CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study were classified as ANI. However, the clinical relevance of this designation is controversial. Gisslen, Price, & Nilsson (2011) suggested an artificial inflation of ANI detection resulting from the high number of scores/tests and false positive errors. Statistical corrections and the use of appropriate norms should be attempted to avoid such inflation, distinguish "true" from erroneous detection of

cognitive impairment and deriving the ANI classification. In favour of an ANI category, it has been suggested that ANI may provide an opportunity to detect early warning signs of impending cognitive deterioration. Therefore, sensitivity to ANI may be of particular importance for preventing further cognitive decline in the phases of the disease that are most susceptible for intervention (Chiao, et al., 2013; Cysique, Bain, Lane, & Brew, 2012). Although there is no standard tool to assess HAND in accordance to the Frascati criteria, the most common approaches are outlined in the next section.

1.1.3. Assessment of Neurocognitive Impairments

Before discussing neurocognitive assessment in HIV, it first should be noted that physical health, drug history, and fatigue have to be taken into consideration when interpreting cognitive test results, as should the effects of neurocognitive functioning on activities of daily living (Cysique & Brew, 2009). It is also important to consider the influence of differences in language, education and culture, especially when applying North American norms to international populations; the HIV population within North America is highly diverse. Even differences in the clade of HIV, primarily dictated by the geographical region of infection, can have an influence on the neurocognitive profile of patients (Sacktor, Nakasujja, Robertson, & Clifford, 2007; Sacktor, et al., 2009). This creates some difficulty in discerning international study results and can influence sample size considerations when not using a homogenous population.

In neuropsychology, a broad, multi-hour assessment of cognitive functions is ideal, especially in a neurologically complicated population. However, because of the inherent risks and complicated nature of HIV, a detailed assessment of neurocognitive functioning is often a secondary concern and simply not feasible due to limited resources (e.g., qualified professionals, time, space, finances).

To address such constraints, conventional dementia screening tools such as the Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Montreal Cognitive Assessment (MoCA) (Nasreddine, et al., 2005) have also been used to detect HAND in HIV populations. However, these screening tools were developed to detect signs of cognitive decline in the context of cortical dementias (e.g., Alzheimer Disease) with cognitive deficits (e.g., naming errors, visuospatial deficits) resulting from posterior neocortical pathology. HIV-associated neurocognitive impairments often preferentially involve fronto-striatal regions, with predominant problems in processing speed (Cherner, et al., 2002; Moore, et al., 2006). Thus, conventional cognitive screening tools, especially the MMSE, are not sensitive enough for detecting HIV-related neurocognitive impairment, especially in current-day HIV populations (McArthur & Brew, 2010; Power, Selnes, Grim, & McArthur, 1995; Skinner, Adewale, DeBlock, Gill, & Power, 2009). The MoCA screening has been reported to be superior to the MMSE in detection of neurocognitive impairment in HIV (Hasbun, et al., 2012; Overton, et al., 2013), but with 63 % sensitivity and 71 % specificity in Overton and colleagues (2013) it still seems

more useful as a first-step screening tool for (rather than a replacement of) more extensive and/or targeted neuropsychological testing.

A few succinct HIV-specific screening tools have been developed, including the HIV Dementia Scale (HDS), International HIV Dementia Scale (IHDS; the global adaptation of the former) and Medical Outcomes Study – HIV Health Survey (MOS-HIV) (Power, et al., 1995; Skinner, Adewale, DeBlock, Gill, & Power, 2009; Wu, Revicki, Jacobson, & Malitz, 1997). Both the original and the international iteration of the HIV Dementia Scale assess memory, attention and psychomotor speed and both were reported to be more sensitive for detecting neurocognitive alterations in a seropositive population than the MMSE (Ganasen, Fincham, Smit, Seedat, & Stein, 2008; Power, et al., 1995). While both HIV Dementia Scales focus on objective measures of cognitive functioning, the MOS-HIV examines the subjective influence of health status on quality of life, perspectives on health and subjective psychological functioning via self-report. Results in self-report scales in HIV should be supplemented by objective test data whenever possible, as they are known to be influenced by neuropsychiatric (rather than or in addition to cognitive) problems, such as depression (Blackstone, et al., 2012). Furthermore, the brief screening tools were not intended to adhere to the Frascati criteria, but to provide an opportunity to systematically assess subjective complaints (MOS-HIV) as well as detect more severe forms of cognitive impairment (HDS, IHDS). The HDS and IHDS have high sensitivity for detecting HAD and supersede the sensitivity of the MMSE, but they also are limited in milder forms of neurocognitive impairment (the ANI category) (Carey, et al.,

2004; Haddow, Floyd, Copas, & Gilson, 2013; Richardson, et al., 2005; C. A. Smith, van Gorp, Ryan, Ferrando, & Rabkin, 2003; Valcour, Paul, Chiao, Wendelken, & Miller, 2011; Zipursky, et al., 2013).

Several suggestions have been put forward to delineate more comprehensive test batteries for the detection of neurocognitive impairment in HIV. Early recommendations by the National Institute of Mental Health (NIMH)-sponsored "AIDS Workshop: Neuropsychological Assessment Approaches" included an extensive (7–9 hour) and a shortened (1–2 hour) neuropsychological battery (Butters, et al., 1990). Refinement of a shortened (1-2 hour) battery was published by Woods, et al. (2004), including seven cognitive domains. The CHARTER study used a slightly different and extended 2.5 hour battery, also spanning seven cognitive domains (Heaton, et al., 2010).

In addition to screenings and multi-domain batteries, single tests have been identified that may be particularly sensitive to cognitive impairment in HIV. For example, the simple addition of the Trail Making Test increased the sensitivity of the IHDS to detect milder forms of HAND from 53% to 86% in a sample of 75 seropositive adults in Bangkok (Chalermchai, et al., 2013). Two studies by Robertson and colleagues used *only* Trail Making Tests A and B and WAIS-R Symbol Digit Modalities and this condensed assessment was sensitive enough to differentiate between patients and controls (Robertson, et al., 2007; Robertson, et al., 2010). Moore and colleagues (2012) reported that a combination of the Stroop Test, Hopkins Verbal Learning Test-Revised and the Paced Auditory Serial Addition Test reached 86% sensitivity and 75% specificity for

detection of neurocognitive impairment in a sample of 200 North American HIV-positive soldiers, when evaluated against a more extensive 2-hour test battery (Moore, et al., 2012). An additional increase in specificity to 87% was achieved with the inclusion of action (verb) fluency. Similarly, another group reported in 104 HIV patients that a combination of three measures of attention and executive function (Trail Making Test A and B, Letter Fluency) showed the highest sensitivity (74.5%) and specificity (81.8%) in detecting neurocognitive impairment, compared against a standardized seven domain 2-hour battery (Munoz-Moreno, et al., 2013). The further addition of tests including all domains, but still restricting administration time to about 35 minutes, led to an even higher sensitivity (100%) and specificity (96%).

In summary, short screenings for HAND are available and in use, but will likely miss milder cases (e.g., ANI) as will screening-tools like the MoCA that were not developed with HIV populations in mind. Single tests with particular sensitivity to HAND seem to be tests of psychomotor speed, attention, executive functions, and memory. Several more extensive neuropsychological batteries spanning five to seven domains of neurocognitive functions seem to be best suited to capture neurocognitive dysfunctions in HIV across a range of severity.

1.1.4. Domains of Neurocognitive Impairment

Involvement of the CNS and brain in HIV is restricted to specific structural sites and the accompanying neurocognitive impairment consequently affects select cognitive domains. Early observations showed that the

neurobehavioral profile of HAND was similar to that of other subcortical pathologies like Parkinson's disease (Berger & Arendt, 2000). Even though the neurocognitive profile in HIV has evolved, there remains a preferential involvement of subcortical-frontal brain regions in HIV (Cohen, 2009). Neurotoxic effects of the virus are prominent in the basal ganglia and frontal cortex, as well as in the connecting white matter tracts. For example, caudate and putamen had higher viral loads than cortical regions in individuals with HAD in early studies (Fujimura, et al., 1997; Wiley, et al., 1998). The basal ganglia show atrophy in advanced-stage HIV (Jernigan, et al., 1993) and in HAD (Aylward, et al., 1993). Caudate volume loss has been correlated with deficits in motor skills, information processing speed, verbal fluency, and complex attention (Kieburtz, et al., 1996). These findings are similar to more recent studies pointing to correlations between cognitive impairment (including episodic memory) in HIV and abnormalities in caudate and putamen (Ragin, et al., 2005). A recent structural MRI study in 92 HIV-patients reported significant correlations between the severity of global brain atrophy, as well as more specifically basal ganglia changes and cognitive impairment (Steinbrink, et al., 2013). In this study, cognitive impairment was significantly correlated with levels of total tau in the cerebrospinal fluid, but not with phospho-tau or A-beta-amyloid, suggesting different underlying mechanisms for HAND and Alzheimer dementia (cf. Morgan, et al., 2013; but see also Soontornniyomkij, et al., 2012).

The most common neurocognitive impairments in HAND are deficits in reaction time and information processing speed, executive function, complex

forms of attention (divided attention, selective attention), and motor speed. Problems with learning and memory, especially with verbal material, are also highly prevalent (Cohen, 2009; Grant, 2008), as are (load-dependent) deficits in working memory and prospective memory (remembering to remember), the latter two memory functions relying on frontal rather than medial temporal lobe regions (Ernst, Chang, & Arnold, 2003; Munoz-Moreno, et al., 2008; Woods, Iudicello, et al., 2008; Woods, Moran, et al., 2008; Wright, et al., 2009). Language impairments are subtle and present mostly as word, especially verb fluency deficits, pointing to problems with executive rather than language functions (cf., Grant, 2008).

Regions other than fronto-subcortical structures and circuits are involved in the HIV pathology, which may result in cognitive impairment above and beyond a clearly 'subcortical' deficit profile.

1.1.5. Factors Associated with Neurocognitive Impairment in HIV

Comorbid factors and individual differences are especially important when discussing an HIV population. Neurocognitive impairment can be influenced by characteristics of the individual, the virus, and treatment.

Individual health status factors such as drug or alcohol abuse or the presence of Hepatitis-C virus (HCV) co-infection can exacerbate impairment; all of which are highly prevalent in the seropositive population (Buxton, et al., 2010; Foley, Ettenhofer, Wright, & Hinkin, 2008; Martin-Thormeyer & Paul, 2009; Vivithanaporn, et al., 2012). Estimates of HCV and HIV co-infection in North

America range from 33 to 53% (Buxton, et al., 2010; Foley, et al., 2008). The CHARTER group, finding 52% of patients with neuropsychological impairment, reported higher cognitive impairment rates in patients with greater comorbidity (e.g., drug use, opportunistic infections). The patient group with the fewest comorbidities showed the strongest correlations between nadir CD4+ T-cell count and cognitive impairment (Heaton, et al., 2010), suggesting that biological measures are most accurate in a less complicated population. Apart from substance abuse and HCV co-infection, additional aggravating factors on the level of the individual include past/present depression and other psychiatric conditions. The HIV/AIDS Costs and Services Utilization Study (HCSUS) study reported that nearly half (48%) of the participating 2864 HIV patients had a probable mental disorder (Burnam, et al., 2001; see also Dew, et al., 1997; Kessler, et al., 2006). Whether via reduced cART treatment adherence (Springer, Dushaj, & Azar, 2012) or via direct effects (Bauer, 2008), mental illness in HIV seems to further promote cognitive deterioration (Anand, Springer, Copenhaver, & Altice, 2010).

Viral differences, including different subtypes of HIV (clades) may also influence neuropsychological findings. While HIV-1 B is the predominant clade seen in North America, Australia and Western Europe, it represents just 12% of individuals infected worldwide (Tashima & Rana, 2009). A study in Uganda, for example, was able to delineate a particular increase in dementia risk in individuals with the HIV-D clade of the virus, compared to individuals with the HIV-A clade (Sacktor, et al., 2009). Genetically distinct variations of the virus should therefore be taken into consideration when assessing presence and severity of HAND and

conclusions drawn from North American studies may not be applicable to all infected groups (Paul, Sacktor, Cysique, Brew, & Valcour, 2009).

A) Biomarkers of HIV and Relationship to Neurocognitive Impairment

Various biomarkers related to HIV have been linked to disease severity and also to neurocognitive functioning. Two of the most common biomarkers investigated in this area are the blood CD4+ T-cell count and plasma viral load (Marcotte, et al., 2003). The two measures are routinely collected by health care providers to determine a patient's immune functioning and response to treatment. The CD4+ T-cell count represents the body's immune response; the lower the count, the worse the immune system is functioning. Health care providers base their decision to initiate treatment largely on this marker. The nadir CD4+ T-cell count, the lowest ever recorded CD4+ T-cell count, has been reported to be one of the most robust biological measures in regards to neurocognitive functioning (Brew, 2004; Cysique & Brew, 2009). The nadir CD4+ T-cell count better represents a person's immune history over the entire disease course rather than their current (treated) state and it is often predictive of immune damage that the disease has caused over the course of infection. For example, in 2011 the CHARTER group showed that the risk of HAND was lowest in patients with CD4+ T-cell counts which had never fallen to low levels before initiation of combination antiretroviral therapy (Ellis, et al., 2011). Plasma level of HIV RNA (i.e., viral load) is another commonly studied biomarker. It represents the amount of HIV virus in the blood. While relationships to neurocognitive functioning are

not as consistent as with the nadir CD4+ T-cell count, current CD4+ T-cell count was a good marker of CNS damage in the pre-cART era or untreated individuals (Brew & Letendre, 2009). Similarly, a recent Canadian study with 1,320 HIV patients at the Southern Alberta Clinic (SAC) in Calgary showed that - in conjunction with older age and longer disease duration - lower nadir CD4+ T-cell counts, and higher viral load (at baseline) significantly predicted the development of neurocognitive impairment (McCombe, Vivithanaporn, Gill, & Power, 2013). A previous study by the same group examined data between 1998 and 2007 and reported that median CD4+ T-cell counts (baseline and nadir) were predictive of neurological impairment and that the worsening of biological measures was associated with significantly higher mortality rates; the presence of HAND also increased the risk for the presence of other neurological issues, such as seizures and death (Vivithanaporn, et al., 2010).

Numerous other biomarkers, not part of the present study, have been reported to correlate with neurocognitive functioning and to improve with treatment. Examples of biomarkers related to the central nervous system include, but are not limited to: β-2-microglobulin, neurofilament-light, higher CSF-to-serum MMP-9 levels, TNF-α and quinolinic acid (see Brew & Letendre [2009] for review). TNF- α, for example, is thought to increase replication of the virus within infected macrophages. Quinolinic acid is both a toxin and represents monocyte activation; it has been correlated with HAD severity and levels return to normal following antiretroviral treatment (Brew & Letendre, 2009).

B) Treatment-Related Factors in Neurocognitive Impairment

In addition to individual and viral differences, the treatment of the illness may also have implications for neurocognitive functioning. Antiretroviral (ARV) drugs used to treat HIV interfere with the viruses' replication process; used in combination, the treatment approach is known as combination antiretroviral therapy (cART) or highly active antiretroviral therapy (HAART)[i]. Each drug in the combination works to block a different aspect or stage of virus replication and infection, preventing virus mutation and increasing the chances of treatment success (Liner, Ro, & Robertson, 2010). Combinations have at least two active drugs from different classes, but usually contain three or more. Since first introduced in the mid-1990s, cART has resulted in an estimated 11.7 million life-added years globally between 1996 and 2008, with 7.2 million of those life-added years in Western Europe and North America (WHO, 2009).

While 11 out of 15 studies reviewed in Joska and colleagues (2010) reported neurocognitive improvement over an average period of six months after initiation of cART, improvement is often partial, variable and most pronounced in patients with lowest baseline performance (Cysique & Brew, 2009; Cysique, et al., 2009; Joska, Gouse, Paul, Stein, & Flisher, 2010). Comparing presence and pattern of neuropsychological impairment before and after cART, two studies by Cysique and colleagues suggested a subtle change in cognitive profiles, even in individuals with undetectable plasma viral load, from less subcortical (e.g., in psychomotor speed) to higher order deficits (e.g., in executive functions and working memory) (Cysique, Maruff, & Brew, 2004; Cysique, et al., 2009).

However, a number of studies also report no changes or even further deterioration of neurocognitive status after initiation of cART treatment. The prevalence of neurocognitive deficits in cART-treated patients was reported to be 20% in Sacktor and colleagues (2002), and deficits had not reversed after a 5-year longitudinal follow-up in more than half of individuals (Sacktor, et al., 2002). Almost 70% of patients in the CHARTER study were on cART treatment in 2010, but as described above, prevalence of neurocognitive problems remained high (52%). Even in patients without confounding or contributing comorbidities, 40% had either ANI or MND status. Robertson and colleagues' results of the ALLRT study (2007) also implied that a substantial proportion of initially cognitively intact patients (21%) may develop cognitive impairment after initiation of cART treatment, although assessment was restricted mainly to processing speed (Trail Making Tests A and B; Symbol-Digit Modalities Test) and practice effects were not controlled.

A variety of theories behind the reason for continued neurocognitive dysfunction despite treatment success have been proposed. Some antiretroviral drugs are known to have neurotoxic effects. For example, efavirenz, approved for use in the late 1990s remains a commonly prescribed ARV as part of a cART regimen. It is associated with an increased risk of depression, memory loss, confusion and psychosis and current guidelines caution its use in individuals with a diagnosis or history of depression or other major psychiatric disease (WHO, 2010). To this end, Ciccarelli and colleagues (2011) reported in 146 HIV patients that among demographic factors (non-native Italian heritage, older age), the

presence of efavirenz in their patients' cART regimens was the single most important predictor for neurocognitive impairment, especially in attention and executive functions (Ciccarelli, et al., 2011). Furthermore, different cART drugs have varying levels of CNS penetrance, numerically classifiable by the CNS penetration effectiveness (CPE)-score (Letendre, et al., 2008). While higher CPE was reported to improve neurocognitive functioning in some studies, the opposite finding has also been reported (Marra, et al., 2009). In Marra and colleagues (2009), 101 patients started or changed to cART regimens with higher CPE scores, effectively lowering CSF viral load. However, drugs with better CPE scores were associated with *poorer* neurocognitive performance, implying higher neurotoxicity with higher CPE. Of note, certain antiretrovirals have been reported to increase the risk for cardiovascular disease, and such drugs in turn have high CPE (e.g., abacavir, lopinavir, indinavir) (Friis-Moller, et al., 2010; Law, et al., 2006). Although cardiovascular disease-related brain damage seems to emerge as a possible factor in HAND (Cruse, Cysique, Markus, & Brew, 2012), direct linkage is currently not available. A qualitative meta-analysis by Cysique and colleagues (2011) came to the conclusion that very few studies investigating effects of cART on HAND had an appropriate design and sufficient number of participants to detect such relationships reliably (Cysique, Waters, & Brew, 2011). In their review, the overall effects of cART on cognition were reported to be positive rather than negative, although only two studies were sufficiently powered. Thus, whether cART has potentially detrimental or beneficial effects on

cognition cannot currently be answered with certainty [see also (Manji, Jager, & Winston, 2013)].

A ‘legacy effect’ of HIV-related brain damage has been proposed; once brain damage has occurred, the associated loss of function cannot be reversed (Brew, 2010). The importance of the *nadir*, i.e., lowest ever, CD4+ T-cell count as a potent predictor of neurocognitive impairment also speaks to such legacy effects.

1.1.6. HIV - Summary

Although there has been a significant decline in the most severe cases of HAND, milder cognitive deficits remain very prevalent or become even more prevalent in an aging HIV+ population. Preferential involvement of fronto-striatal and limbic regions matches well with predominant deficits in psychomotor speed, attention, executive functions, and memory. If tested, assessment of dysfunctions is often done with succinct screenings, but to fully delineate the range and severity of HAND testing should extend to multi-domain neuropsychological test batteries. Direct and indirect effects of HIV medications on cognition are currently not clear, although evidence for both supportive and detrimental effects of (certain) drugs exists. Biological markers of disease severity that are most closely linked to HAND include CD4+ T-cell count (nadir more so than current CD4+ T-cell count) as well as viral load (CSF>plasma).

The current study focuses on a particular cognitive function that has rarely been studied in HIV positive individuals: Decision making.

1.2. Decision Making

Making advantageous decisions is fundamental to the ability to function as self-sufficient individuals. The number of decisions people make in any given day is immeasurable. From deciding between a salad or a cheeseburger for lunch to the choice between two career directions, problems with decision making will influence our life in many ways.

From a neuropsychological perspective, decisions can be divided into decisions under *risk* and decisions under *ambiguity*. In risky decision making situations, the potential outcomes and their probabilities are available, so that decisions can, in principle, be made by using this information. For example, one is told that a hypothetical tropical fruit is well known for its superb taste, but that it also has a 40% chance to induce vomiting. One can then decide whether to risk vomiting or risk missing out on tasting that fruit and which one of the two options is more advantageous. In ambiguous decisions, such outcomes and probabilities are not apparent. In such situations, implicit information or other emotional hunches associated with a choice option must be relied on. To stay within the example, suppose one had eaten the tropical fruit as a very small child, and had vomited. At present, one is not given further information about the fruit and also has no explicit memory for the initial encounter with the fruit (or the consequences). Yet, when offered to taste the fruit, one might have a faint feeling of uneasiness and decide not to try. In this case, one was faced with an entirely ambiguous decision but an instinct or implicit memory guided the current decision, in this case, not to risk trying the fruit.

1.2.1. Decision Making Under Ambiguity – Iowa Gambling Task

The Iowa Gambling Task (IGT) is the most commonly used neuropsychological decision making task (Bechara, 2004; Gleichgerrcht, Ibanez, Roca, Torralva, & Manes, 2010). It was designed by Antoine Bechara and colleagues (Bechara, Damasio, Damasio, & Anderson, 1994) to measure decision making under ambiguity and to mimic real-life decision making challenges in patients with relatively focal lesions to the ventromedial prefrontal cortex (PFC). The patients were unimpaired in classic executive function tests such as the Wisconsin Card Sorting Test. The IGT has participants choose between one of four decks (A-D) and instructs them to maximize their winnings. Each deck is stacked in a predetermined pattern to produce a specific frequency and size of gains/losses. Unknown to the participants, two decks (A and B) are disadvantageous in the long run insofar as they are associated with high immediate wins, but frequent (deck A) or infrequent (deck B) losses that supersede the wins. The other two decks are advantageous as they yield low wins but even lower frequent (deck C) or infrequent (deck D) losses. Cards are drawn one at a time for 100 trials. Over the course of the task, most healthy individuals implicitly acquire the rules and contingencies and start to prefer decks C/D over A/B. That is, through cycles of reward and punishment feedback associated with each decision, individuals are meant to start avoiding disadvantageous decks and learn to prefer advantageous decks. The IGT is primarily meant to measure decision making under ambiguity as the decider is not given any information

about size, frequency and probability of possible rewards or punishments associated with each card deck and does not know how long they can play.

Patients with ventromedial/orbitofrontal cortex lesions do not learn from feedback in this task and continue to make disadvantageous decisions (Bechara, et al., 1994; Bechara, Damasio, & Damasio, 2000; Bechara, Tranel, & Damasio, 2000). Interestingly, healthy individuals (but not patients with ventromedial PFC lesions) show an increase in skin conductance before making a risky (A/B) decision in the IGT, an emotional arousal reaction that occurs even prior to explicit knowledge about the odds (Bechara, Tranel, Damasio, & Damasio, 1996). Patients with bilateral amygdala lesions are also impaired in the IGT and show a lack of the normative preparatory skin conductance increases (Bechara, Damasio, Damasio, & Lee, 1999). Thus, the IGT is usually understood as a measure of primarily emotional elements of decision making (as was intended in its design), although working memory and fluid intelligence also play a role in IGT performance (Dunn, Dalgleish, & Lawrence, 2006; Gleichgerrcht, et al., 2010). However, later occurring trials of the IGT (e.g., the 100 trials of the IGT are often subdivided into 20-trial blocks), such as trials from task blocks 3-5 seem to also measure executive functions (Brand, Recknor, Grabenhorst, & Bechara, 2007b). That is, once the contingencies between the card decks and reward/punishment are learned, emotional feedback (i.e., reward/punishment) becomes less essential to guide further decisions. In this sense, only early IGT trials truly measure decision making under ambiguity, while later trials may also assess decision making under risk. The IGT is a very complex task, and it has been criticised for

its lack of specificity as impairment in the IGT can occur for a variety of reasons, not all of them (neuro-)pathological (see Dunn, et al. [2006] for extensive review). Thus, if impairment in the IGT arises, it is not always clear why someone does not learn to make advantageous decisions (Dunn, et al., 2006; Maia & McClelland, 2004).

1.2.2. Decision Making Under Risk – Game of Dice Task

There are several neuropsychological tests for the assessment of decision making under risk, i.e., decisions that are made with the explicit provision of rules and probabilities of possible outcomes of decisions. Among the most common are the Cambridge Gambling Task (Rogers, et al., 1999) and the Game of Dice Task (GDT, Brand, et al., 2005a), of which the GDT is the focus of this thesis. A more extensive description of the GDT is given in the Methods section (2.2.12). In brief, in the GDT asks participants to maximize winnings over an 18-cycle course of selection and feedback. The goal is to have one rolled die (computer generated) match one of the dice in the participant's selection. During each round, the same 14 different selection options and corresponding reward/punishment levels (4) are presented (see Figure 2.8 in the Methods section). Each selection option is comprised of one, two, three or four dice combinations which directly relate to level of risk and the explicit amount of reward or punishment – riskier selections present higher potential reward/loss and safer options provide lower reward/loss. For example, a single-die selection has a 1:6 probability of returning a win of $1,000 versus the four-dice option which returns just $100 but with the higher odds of 2:3. As the GDT is designed to measure decisions under risk, information

regarding reward contingencies is explicitly displayed to the participant throughout the task. The most common quantification of GDT performance is the *net-score* which is the overall task performance across all trials; it is obtained by subtracting the number of risky choices from non-risky choices. Task performance can also be analyzed across task blocks by dividing the 18 trials into three equal groupings of 6 trials (trials 1-6, 7-12, and 13-18) to delineate performance over time. Performance patterns can also be examined by quantifying how participants change their selection habits from risky to safe choices (or vice versa) in response to feedback. This is referred to as shifting. The frequency with which each level of risk is selected is another performance measure in the GDT, as are the amount of money won in the task, and expected values for each decision. Section 3.2 describes the GDT scores used in this thesis in greater detail.

The GDT provides feedback after each trial to the participant, but unlike the IGT, feedback is not necessary to complete the task. Using a healthy population, Brand (2008) demonstrated that while the provision of feedback significantly increased task performance, its omission did not make the task impossible to complete. In both the original GDT and the version without feedback, performance was related to executive functions. Thus, while executive functions covary with GDT performance, the provision of feedback is also important although less so than in the IGT.

The neurocognitive domain most robustly correlated with decision making is executive functioning (Brand, et al., 2005a; Brand, Laier, Pawlikowski, &

Markowitsch, 2009; Brand, et al., 2007b). A 2011 study by Schiebener et al. examined the role of executive function, feedback and categorization of probabilities using the GDT, IGT and a Probability Associated Gambling Task. The study reported that the ability to manage and understand probabilities, executive functions and logical thinking (fluid intelligence) played a critical role in GDT performance (Schiebener, Zamarian, Delazer, & Brand, 2011). A study by Brand and colleagues (2004) in Parkinson's disease patients revealed that patients with intact executive functioning and feedback processing performed the task best (Brand, et al., 2004). In addition, Brand et al. (2008) revealed that individuals who make use of calculative (versus intuitive) decision strategies were more likely to perform well on the GDT and to shift less frequently. The use of calculative strategies in turn was related to executive function measures but not to IGT performance (Brand, Heinze, Labudda, & Markowitsch, 2008). Relationships between GDT and age have also been reported previously. Brand and Schiebener (2013) reported that increasing age will lead to reductions in GDT performance, but only in individuals with lower fluid intelligence levels (logical thinking) and in individuals with lower executive functions.

A variety of patient populations have been reported impaired in the GDT, including neurological conditions [Korsakoff's Syndrome (Brand, et al., 2005a), Alzheimer's disease), Parkinson's disease (Brand, et al., 2004; Euteneuer, et al., 2009)], and psychiatric diseases [pathological gambling (Brand, et al., 2005b), bulimia nervosa), binge eating disorder (Svaldi, Brand, & Tuschen-Caffier, 2010), opiate addiction (Brand, Roth-Bauer, Driessen, & Markowitsch, 2008) and

schizophrenia (Fond, et al., 2013, but see. Lee, et al., 2007)]. The impairment does not always present in the same way. For example, in two studies that compared Parkinson's disease patients with pathological gamblers, Parkinson's patients tended to choose the riskiest GDT option, whereas pathological gamblers preferentially selected both risky options (single die and two-dice options); furthermore, Parkinson's patients began their performance in this manner, while gamblers moved towards riskier options as the task progressed (Brand, et al., 2005b; Brand, et al., 2004).

In summary, unlike the IGT, the GDT provides risks and probabilities upfront and therefore allows for the development and maintenance of an explicit decision strategy. The GDT has been more consistently related to executive functions than the IGT, and does not require splitting up task trials to evaluate potential shifts from decision making under ambiguity versus risk as is sometimes done with the IGT. The GDT has revealed deficits in decision making under risk across many neurological and psychiatric conditions, but has never been applied to HIV patients. Therefore, the GDT was used here to delineate the understudied function of risky decision making in a HIV+ population.

1.2.3. Neurobiology of Decision Making

Decision making is a complex process that can be deconstructed into several sub-processes. On the basis of human functional neuroimaging and patient studies, three primary components of the decision process have been proposed by Gleichgerrcht, et al., (2010): 1) a *stimulus encoding system*, where

the value of each potential choice is assigned - this system involves orbitofrontal cortex and ventromedial PFC; 2) an *action selection system* responsible for selecting one of the options - this system is associated with the anterior cingulate cortex, lateral PFC and parietal cortices; and 3) an *expected reward system* that reconciles feedback and experience with the selection - this system relies on the basal ganglia (ventral striatum), and limbic areas including the insula and amygdala. A similar model including also animal data and neurochemical evidence is proposed by Doya (2008).

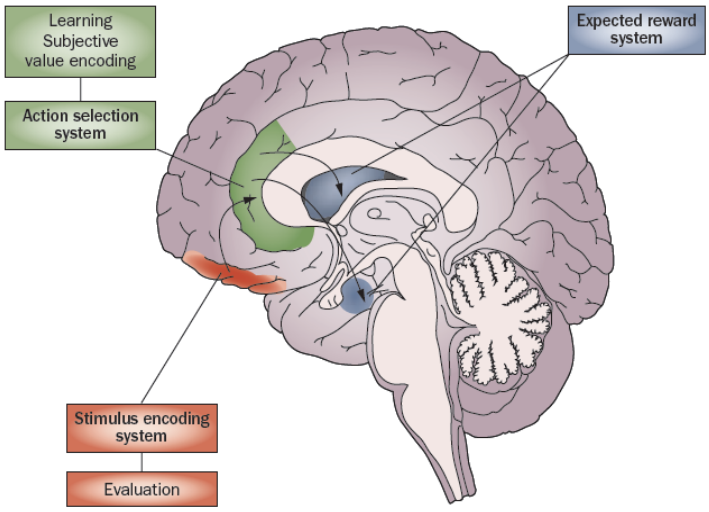

Figure 1.2. Neuroanatomical model of decision making. Stimulus encoding system (red): orbital frontal cortex; action selection system (green): anterior cingulate cortex; expected reward system (blue): basal ganglia and amygdala (Gleichgerrcht, et al., 2010).

These systems are reciprocally connected and (behavioural/neural) dysfunction in one aspect of decision making can disrupt functions in others. For example, Bechara and colleagues (2000) proposed that ventromedial PFC lesion

(*stimulus encoding system)* patients' failure to make good choices in the IGT might be caused by a failure to integrate bodily arousal signals from limbic and insula regions within the ventromedial PFC. Impairments in the IGT in patients with insula damage (Clark, et al., 2008), or amygdala damage (Kobayakawa, Koyama, Mimura, & Kawamura, 2008), as well as in patients with dopaminergic dysfunctions of the midbrain and basal ganglia (e.g., Parkinson's patients) (Pignatti, et al., 2012; Sevy, et al., 2006) speak to a possible disturbance in the *expected reward system* involved in the decision making process as suggested by Gleichgerrcht and colleagues (2010).

Neurophysiological studies in monkeys reported stimulus value coding in neurons in the orbitofrontal cortex during choice tasks, although inference should be made cautiously due to differences between human/monkey tasks and anatomy (Padoa-Schioppa & Assad, 2006). In human fMRI studies, healthy individuals' blood-oxygen-level- dependent (BOLD) activity in the ventromedial PFC seems to correlate specifically with the stimulus encoding system of the decision making process. For example, Hare, O'Doherty, Camerer, Schultz, and Rangel, (2008) designed an fMRI task that was able to segregate three basic decision-making components: stimulus values, stimulus costs, and (reward) prediction errors. Activity in the medial orbitofrontal cortex correlated with stimulus values (*stimulus encoding system*), and activity in the ventral striatum correlated more strongly with reward prediction errors (*expected reward system*) (see also Plassmann, O'Doherty, & Rangel, 2007). In addition, a similar region within the medial orbitofrontal cortex was reported in Levy, Snell, Nelson, Rustichini, and

Glimcher (2010) to be specifically involved in stimulus value encoding under conditions of decision ambiguity (i.e., incomplete knowledge about the odds. However, a recent meta-analysis of 206 human fMRI studies assessing the representation of stimuli with a subjective value reported that the ventromedial PFC, together with the anterior ventral striatum were both positively activated during receipt or anticipation of subjectively high valued stimuli (e.g., food, monetary rewards) (Bartra, McGuire, & Kable, 2013). The authors suggested that *both* regions may represent a domain-general signal of subjective value that may aid value-based decision making. Findings emphasize the difficulty in segregating component processes of decision making insofar as the proposed systems are meant to and will act in concert in healthy individuals.

Focal damage to either insula or ventromedial PFC can impair decision making under risk. Clark and colleagues (2008) compared performance in the Cambridge Gabling Task (Rogers, et al., 1999) across three groups of focal lesion patients (insula, ventromedial PFC, dorsolateral PFC) and healthy controls. In this task, participants are asked to either bet or withhold betting a stack of points in trials with varying odds of winning, with the goal to increase their point capital. Unlike in the GDT, premature termination of the CGT (the most definitive sign of risk taking in the CGT) occurs when participants gambled away all their points. Another difference to the GDT is that in the CGT odds change in each trial. Thus, participants do not need to develop and maintain a long-term strategy of choosing most favourable odds. This study reported both patients with lesions in the insula and in the ventromedial PFC were impaired in the CGT. Patients with insula

damage were more willing to bet and disregarded the odds altogether, also resulting in significantly higher rates of bankruptcy in patients overcontrols. Patients with ventromedial PFC damage were overall more willing to bet than controls but were able to reduce their betting with decreasing odds. In this study, patients with dorsolateral PFC lesions were not impaired in the CGT.

Areas of the *action selection system,* according to the model of Gleichgerrcht and colleagues (2010) comprising anterior cingulate, lateral PFC and parietal cortex regions, are more closely associated with modulatory and regulatory processes of decision making. Processes include resolving response conflicts between different choice options, inhibition of inappropriate decision responses and monitoring overall task progress. Brain areas of the *action selection system* are particularly involved in decision making under risk, that is, situations in which a clear conflict between choice options and "inappropriateness" of responses can be appreciated (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). In this regard, a useful extension of the GDT has been to eliminate the feedback component as was done in an fMRI study by Labudda and colleagues (2008) in healthy elderly. Authors reported that performance was associated with activity in dorsolateral PFC, posterior parietal and anterior cingulate cortex (i.e., areas of the *action selection system*), rather than ventromedial PFC/orbito-frontal cortex or the limbic/subcortical areas associated with the other two systems (Labudda, et al., 2008).

It should be re-emphasized here that there are reciprocal connections between ventromedial and dorsolateral PFC regions and previous fMRI studies

have also reported an involvement of the dorsolateral PFC during stimulus valuation in decision making tasks (Sokol-Hessner, Hutcherson, Hare, & Rangel, 2012). An interesting recent finding in this regard comes from a study by Hutcherson, Plassmann, Gross, and Rangel (2012). This study tested healthy young participants who were fasting for four hours prior to the experiment. Participants were presented with 150 pictures of common snack foods and asked to deliberately down- or upregulate their food cravings to each picture before they performed a betting task related to the displayed foods. The betting task involved placing a bid between $0 and $2.50 in $0.50 increments for their right to eat the particular food at the end of the test session. Results showed that *both* ventromedial and dorsolateral PFC regions were involved in stimulus valuation at the time participants made their bet. However, in a condition requiring craving down-regulation, activation was decreased in a dorsolateral PFC region relative to one in the ventromedial PFC, implying control or modulation of the incentive value via the dorsolateral PFC.

In summary, a wide range of areas in the brain are associated with component processes of decision making. Core areas of interest concern the ventral striatum as part of the reward system of the brain, limbic areas related to emotional processing, orbitofrontal/ ventromedial PFC regions associated with representation of subjective values, especially so under conditions of ambiguity, (dorsal) areas of the anterior cingulate gyrus concerned with decision conflicts, and the dorsolateral PFC associated with control/inhibition of inappropriate decisions or urges thereof.

The HIV-related preferential involvement of subcortical-frontal lobe regions of the brain represents a particularly interesting pathological backdrop from which to study decision making impairment. Previous findings of decision making in HIV+ are described in Section 1.3.

1.3. Decision Making in HIV+

A few studies have investigated decision making in HIV+ individuals. The following discussion is restricted to studies listed in Table 1.1, all of which used neuropsychological decision making tests. It does not include studies testing single component processes of decision making (i.e., reward processing) in HIV. All published neuropsychological decision making studies in HIV used the IGT to assess decision making under ambiguity, and one study additionally used the Cups Task (Weller, Levin, Shiv, & Bechara, 2007) as a measure of decision making under risk.

Table 1.1. HIV+ Decision Making Studies

Study	Participants	Biological Correlates	Comorbidities	IGT and other variables	Key Findings
Martin, et al. (2004).	*47 HIV- controls* Male: 100% Age: 47.2 yrs. Edu.: 13.1 yrs. *46 HIV+ patients* Male: 100 % Age: 46.2 yrs. Edu.: 12.9 yrs.	CD4 current (med.): 521 Undetectable viral load: 31% (threshold: 400 copies/ml) AIDS: 10% ART: 80% cART: 50%	*All participants:* Substance dependent (past or current): e.g., polysubstance dependence: 85%, intravenous drug use: 60% *Patients:* Cocaine use was slightly more common, but fewer years of dependence and more days of abstinence HCV not assessed	IGT *Net-score* *Net-score per IGT task block* IQ Working memory Sensation seeking Mood Clinical interviews and questionnaires	Patients were impaired in the IGT net-score across all blocks IGT was unrelated to all assessed variables IGT was better in cART treated patients than in untreated patients and in individuals treated with RTIs only.
Hardy, et al. (2006).	*19 HIV- controls* Age: 47.6 yrs. Edu.: 13.9 yrs. *67 HIV+ patients* Age: 43.8 yrs. Edu.: 12.7 yrs. *All participants:* Male: 66% Patients were significantly less educated than controls	CD4 current: 399 AIDS: 58% cART: 100%	*Controls:* Past (time undefined) substance dependence: 4% *Patients:* Current substance dep.: 7.5% Past substance dep.: 43% Patients were more depressed than controls No HCV Analyses controlled for current substance dependence, past substance dependence and mood	IGT *Net-score* *Selections from decks A,B,C,D* *Deck B selections by IGT task block* Attention Processing speed Executive functions Memory Motor functions Mood	Patients were impaired in: IGT net-score (all blocks) Deck B and C selections Deck B selections in blocks 3-5 IGT net-score was unrelated to all assessed variables Deck B selections (all blocks) correlated with executive functions (Stroop Test) and memory (CVLT)

Study	Participants	Biological Correlates	Comorbidities	IGT and other variables	Key Findings
Gonzalez, et al. (2005)	*154 HIV- controls* Age: 43.7 yrs. Edu.: 12.4 yrs. *109 HIV+ patients* Age: 44.6 yrs. Edu.: 12.3 yrs.	CD4 current (med.): 454 AIDS: 19% Undetectable viral load: 33% ART: 82% cART: 41%	*All participants:* Polydrug users (96% dep. and 4% abuse); 97% polydrug dep./abuse. 92% heroin and/or cocaine dep.; 77% cocaine, 65% alcohol, 53% heroine HCV prevalence was not reported, but controlled statistically	IGT *Net-score* *Net-score per IGT task block* *Selections from decks A,B,C,D* Risky sexual practices questionnaire (outcome variable) IQ Working memory Attention Response inhibition Mood Clinical interviews and questionnaires including sensation seeking	Risky sexual practices were predicted by serostatus, all risky choices in the IGT, and self-reported sensation seeking. Only in *good* IGT performers: Sensation seeking predicted risky sexual practices
Thames, et al. (2012)	*26 HIV- controls* Age: 46.31 yrs. Edu.: 14.16 yrs. *100 HIV+ patients* Age: 43.8 yrs. Edu.: 13.08 yrs. Patients had significantly lower pre-morbid IQ than controls (measure and means were not reported	Current CD4: 361.5 Undetectable viral load: 33%	*Controls*: 31% past substance abuse *Patients*: 61% past substance abuse Patients had significantly greater mood disturbances No HCV Analyses controlled for substance dependence and IQ	IGT *Learning index: Net-score from blocks 3-5 minus net-score from blocks 1-2* Processing speed Attention Memory Verbal fluency Working memory Executive functions Motor functions *Note: Composite cognitive domain scores based on published norms.*	Patients were intact in all cognitive domains. IGT learning index was impaired in patients. Executive functions and depression predicted IGT learning index. Depression partially mediated the relationship between executive functions and IGT.

Study	Participants	Biological Correlates	Comorbidities	IGT and other variables	Key Findings
Iudicello, et al. (2013)	*51 HIV- controls* Age: 40.8 yrs. Edu.: 13.2 yrs. *78 HIV+ patients HAND-* Age: 42.9 yrs. Edu.: 13.2 yrs. *68 HIV+ patients HAND+* Age: 43.8 yrs. Edu.: 13.0 yrs. IQ: HAND+ < HAND- = controls	*HAND-:* CD4 current: 462 CD4 nadir: 200 Undetectable viral load: 41.1% Duration: 8.6 yrs. *HAND+:* CD4 current:435.5 CD4 nadir: 160 Undetectable viral load: 46.8% Duration: 7.5 yrs.	*All participants:* Depression (HAND+ > HAND- = controls) Drug dependence (HAND+ = HAND- > controls) *Patients:* HCV co-infection (HAND+ > HAND-) Analyses controlled for depression, substance dependence, HCV co-infection, but not for IQ	IGT *Net-score per IGT task block* *Net-score in blocks 3-5 only* Processing Speed Attention Working memory Executive functions Memory Motor functions Activities of daily living *Note: HAND status was determined with composite cognitive domain scores based on published norms*	Controls and HAND- were similar in all five blocks of IGT. HAND+ were worse than both other groups in blocks 3-5. *All patients:* IGT net-score in blocks 3-5 was related to executive functions & memory; less so to working memory and motor functions HAND status, but not IGT predicted employment status and activities of daily living.
Martin, et al. (2013)	*23 HIV- controls* Age: 47.6 yrs. Edu.: 15.0 yrs. *56 HIV+ patients* Age: 47.9 yrs. Edu.: 14.3 yrs.	CD4 current: 514 CD4 nadir: 271 Undetectable viral load: 59% ART: 93%	*All participants:* Current or past substance dependence HCV was not explicitly mentioned	IGT *Net-score* *Selections from decks A,B,C,D* *Net-score per IGT task block* Cups Task - *Expected value* - *Domain (loss vs. gain trials)* IQ Executive functions Memory Mood Clinical interviews and questionnaires including sensation seeking	Patients were impaired in the IGT net-score, significantly so only in IGT blocks 1-3 Patients were unimpaired in the Cups Task IGT and Cups Task were uncorrelated. Stroop interference correlated with IGT net-score in blocks 4&5, but not with Cups Task. Memory (RAVLT) was negatively correlated with risk taking in the Cups Task

ART: antiretroviral therapy; cART: combination antiretroviral therapy; CD4: CD4+ T-cell count; dep.: dependence; Edu.: Education; yrs.: years; RAVLT: Rey Auditory Verbal Learning Test; HAND+: HIV-patients with neurocognitive disorder; HAND-: HIV- patients without neurocognitive disorder; HCV: Hepatitis-

C virus co-infection; IGT: Iowa Gambling Task; IGT decks: [A & B]: Disadvantageous, [C & D]: Advantageous; IGT net-score: good deck (C and D) choices minus bad deck (A and B) choices; IQ: Intelligence quotient. **Note:** (Gonzalez, Wardle, Jacobus, Vassileva, & Martin-Thormeyer, 2010) and (Wardle, Gonzalez, Bechara, & Martin-Thormeyer, 2010) were omitted from this table as these studies included no control group and were not focused on HIV+ and decision making.

Martin and colleagues (2004) studied decision making and cognitive impulsivity in male participants with past or present substance dependence (predominantly amphetamine/cocaine/heroin) and either concurrent HIV infection (HIV+ : N= 46) or without concurrent HIV infection (HIV- : N= 47) (Martin, et al., 2004). All participants had a minimum of 10 years of education. In the HIV+ group, 80% of the patients were on ART and 50% were on cART. Undetectable viral load was present in just 31% of subjects, indicating unsuccessful immunosuppression in a majority of the patients in this study. In addition to the IGT, the study assessed sensation seeking, current depressed mood, past and current PTSD and ADD symptoms, IQ, as well as working memory performance using a delayed-match-to sample task. Although both groups displayed a linear decline in risky-choice selection, performance on the IGT was overall significantly worse in the HIV+ group. There were no differences in IGT performance in groups of patients with detectable compared to undetectable viral load. Individuals on a cART regimen performed better than individuals on RTIs/untreated. There was no relationship between IGT and psychopathology or working memory in either one of the two groups. It is important to note that there were significant differences between the two groups with regard to severity of substance abuse, although the differences were in favour of the HIV+ group who reported a shorter abuse duration and longer time of abstinence. Surprisingly, HCV co-infection was not reported in this study despite the large proportion of intravenous drug users in both groups.

A study by Hardy and colleagues (2006) included 67 HIV+ individuals and 19 HIV- controls with the focus of ascertaining differential performance in the IGT and correlations to other domains of cognition. Small, but significant differences on the Beck Depression Inventory and education level existed between the HIV+ and control group. A small subset met the DSM-IV criteria for current drug dependence; 43 HIV+ and 4 HIV- met criteria for past drug dependence. When examining performance on the IGT, significant differences between groups on deck selection were reported for disadvantageous deck B and advantageous deck C, but not for decks A or D. HIV- selected more cards from deck C and HIV+ selected more cards from deck B. Overall task performance did not relate to measures of the neuropsychological test battery. Number of choices from deck B was related to Stroop performance and learning in the CVLT in the HIV+ group only, suggesting a potential influence of executive and memory problems to decision making deficits in HIV. The pre-existing differences between patients and controls, including the differences in sample size, education levels, substance use, and concurrent mood symptoms complicate the results, as not all of the variables were controlled statistically.

A study by Gonzalez and colleagues (2005) also used the IGT, although the focus of this study was to find predictors of risky sexual practices in a HIV+ (n=109) and control population (n=154). In addition to the IGT, measures of executive functions and sensation seeking were included. All subjects had a history of substance dependence with nearly all classified as polydrug users (97%). In the HIV+ group, 82% were on some form of HIV treatment and 41%

were on cART. Only 33% had undetectable viral loads. In this study, sensation seeking was related to risky sexual practices, and a trend finding involving the IGT indicated that this was especially true for individuals with *good* performance on the IGT. The authors interpreted this counterintuitive finding as possibly related to the ability to evaluate and appreciate emotional information was essential to perform well in the IGT, in accordance to Bechara's model. That is, only in this case, *good* IGT performance would also increase risk-taking behaviour that was similarly driven by emotional behaviour such as sensation seeking. A later study by the same group (Gonzalez et al., 2010) investigated the relationship between procedural learning and decision making in 49 HIV+ individuals with a history of substance dependence (Gonzalez, et al., 2010). Procedural learning has been linked to the integrity of the basal ganglia in many studies and was expected to play a role in the implicit acquisition of information about decision contingencies in the IGT (Yin & Knowlton, 2006). No control group was included in this study. The authors reported no relationship between IGT and learning in three procedural memory tasks, even when IGT performance in only the earlier task blocks (i.e., blocks in which implicit learning processes predominate) was analysed.

More recently, Thames and colleagues (2012) conducted a study in 100 HIV+ and 26 healthy controls to examine the relationship between depression and IGT performance relative to HIV status. The HIV+ group had significantly more historical substance abuse, and lower pre-morbid intelligence. Performance on a standard neuropsychological battery was not significantly different between the

two groups when IQ was controlled for. Performance in the IGT was calculated with a learning index, subtracting the average number of choices from the advantageous cards (decks C and D) in the first two blocks of trials (trials 1-40) from the average number of advantageous choices in the last three blocks (trials 41-100). The last task blocks in the IGT represent a mixture of decision making under ambiguity and risk, depending on the point at which an individual has reliably acquired the decision rules. Thus, the learning index as calculated here was meant to represent a combination of emotional factors and executive functions contributing to IGT performance. The authors reported a significant difference between the two groups in IGT learning index, controlling for substance use and IQ differences. In both groups, the IGT learning index was positively correlated with attention, working memory and executive functions, while depression was negatively correlated with the IGT learning index. In a mediation model addressing the relationships within the HIV+ group only, depression was reported to partially mediate the relationship between executive functions and IGT learning index. Thus, when IGT was analysed this way, both depression and executive functions were substantially related to decision making deficits in patients with HIV. Given that the HIV patients were overall cognitively intact and there were substantial differences in comorbid depression between the two groups, an additional control group of only depressed patients would be informative to more definitively disentangle the contributions of depression versus executive functions to IGT performance.

Iudicello and colleagues (2013) were interested in examining decision making and its relationship to the presence or absence of HAND. The study used three groups, 51 HIV-, 68 HIV+ with HAND, and 78 HIV+ without HAND. A significantly greater proportion of HAND+ group had HCV and there were group differences for HIV+ patients and healthy controls (in favour of the control group) regarding substance dependence, depression, and IQ. This study reported significant differences across groups in IGT performance. Specifically, an interaction between group and performance per IGT task block emerged, even when controlling for depression and substance dependence. This interaction showed that the HAND+ group performed worse than the HAND- group and the control group on IGT task blocks three to five but not in earlier task blocks. HIV- and HAND- groups performed similarly across IGT task blocks. Performance in the final three IGT task blocks in all HIV (HIV+ HAND+ and HIV+ HAND-) patients was predicted by performance in composite scores of neuropsychological function derived from population norms. The executive function composite score consisting of two measures of cognitive flexibility (Trail Making Test B-A and WCST perseverative responses) remained the only significant independent predictor of IGT task block 3-5 performance. Finally, IGT performance was also examined as a possible predictor of functional outcomes in this study (independent living, employment, medication adherence), but failed to show significant predictive value over and above HAND status, AIDS diagnosis and ARV medication status.

Martin and colleagues (2013) tested decision making with two tasks in a sample of 56 HIV+ and 23 HIV- men who have sex with men. All individuals had a history of substance dependence. Unlike all previous studies, in addition to the IGT, this study also included a task measuring decision making under risk, the Cups Task (Weller, et al., 2007). Briefly, in the Cups Task participants receive a computerized block of "gain" trials and a block of "loss" trials. On each trial, the participant makes a choice between safe gains/losses of a quarter hidden underneath a cup. The alternative choice is a gamble for larger (versus no) gains in gain trials and for no (versus larger) losses in loss trials. The probabilities for gambles are indicated on the computer screen by the number of cups associated with the risky choice. That is, the participant can estimate the likelihood of each outcome and therefore, the Cups Task is meant to measure decision making under risk. Similar to the CGT and unlike the GDT, the odds for winning/losing change in each trial of the Cups Task, so no consistent multi-trial decision strategy has to be developed and followed. The HIV+ group in Martin and colleagues (2013) performed worse on the IGT than the HIV- group, but both groups were identical in the Cups Task. Unlike in Iudicello and colleagues (2013) and Thames and colleagues (2012), the HIV+ subjects here tended to perform more poorly during the *early* IGT trials, i.e., when uncertainty about specific outcomes was greatest. However, similar to these former two studies, performance on the final task blocks (here: IGT blocks four and five) was significantly correlated with executive functions (Stroop Interference). Self-reported severity of substance abuse did not change most of the differences in IGT performance between groups,

with the exception of opioid addiction which rendered the group difference a trend effect ($p=0.055$).

In summary, existing studies on decision making in HIV point to deficits in the IGT. Studies analyzed the IGT differently, but the largest studies point to a particular impairment in the last sections of the IGT. As noted previously, performance on later IGT trials measures decisions making under risk in addition to or instead of decision making under ambiguity. Therefore, the few studies finding relationships between IGT and executive functions are to be expected. However, the only study that examined decision making under risk in HIV did not find significant impairments in patients. Of note, all of the HIV subjects in these studies were complicated by substantial past or present substance abuse, HCV co-infection, or demographic differences mostly in favour of the control groups (IQ, education), which causes difficulties in a clear interpretation of results. Furthermore, even though (some) biological parameters indicating patients' current HIV status and severity were reported in all studies, but were never analysed directly in their relationship to decision making.

Thus, the current study investigated differences between HIV + and HIV – individuals in decision making under explicit risk. The current study used the GDT, which has never been used in HIV and represents a decision making tool with known correlations to executive functions. Eliminating as many confounds as possible, the study used a population free of substance use, no history of HCV co-infection and a healthy control group matched on demographic and educational background.

1.4. HYPOTHESES

Hypothesis 1: The HIV+ group will display deficits in neuropsychological testing compared to the healthy control group, especially in motor functions, processing speed, attention and executive functions.

Hypothesis 2: The HIV+ group will have poorer performance in decision making under risk as assessed with the GDT, compared to the healthy control group.

Hypothesis 3: Performance on the GDT will co-vary with biological markers of disease severity (e.g., nadir CD4+ T cell count) and cognitive, especially executive functions in HIV patients.

2. METHODS

2.1. Participants

The study was approved by the Health Research Ethics Board at the University of Alberta. Individuals with HIV+ infection were recruited from two clinics, the Northern Alberta Clinic in Edmonton and the Southern Alberta Clinic in Calgary, with the help of Drs. Christopher Power, Stanley Houston (Department of Medicine, University of Alberta), and John Gill (Department of Medicine, University of Calgary). Healthy controls were recruited by print/online advertisements in Edmonton's Metro Newspaper and Edmonton's Kijiji Classifieds. HIV+ serostatus was confirmed via consultation of medical records in the clinical group only. All study participants were screened for possible study confounds through a health status background questionnaire. The screening was either delivered over the phone or in person (in the clinics). An overview is given in Table 2.1.

Table 2.1 Exclusion Criteria for All Participants

- Acquired or congenital brain damage (e.g., epilepsy, stroke, moderate to severe head trauma, dementia, Parkinson's disease)
- Hepatitis C virus infection (HCV)
- Major neuropsychiatric illnesses (co-morbid or previous; e.g., major depression, psychosis or any others requiring hospitalization)
- Psychotropic medication (low dose antidepressants, anxiolytics, and analgesics, e.g., gabapentin were not exclusionary)
- Abuse of alcohol, illicit or prescription drugs within past 5 years, injection drug abuse at any time. Mild-moderate use of marijuana or alcohol more than 5 years ago was permitted as was recreational (less than 2-3 x/year) use of other substances.
- Uncorrected sensory deficits (i.e. vision and hearing)
- Developmental disabilities

- Non-fluency in English
- Age less than 18 or greater than 60

A total of 24 HIV+ patients were recruited and tested. Four patients had to be excluded. In two patients, details on their psychiatric and health histories (current drug abuse, head trauma) became available only after the testing. One patient was illiterate. One patient was very depressed/fatigued and their partial data was excluded. The final sample consisted of twenty HIV+ individuals and twenty healthy controls, characteristics are summarized in Results Table 3.1.

2.2. Materials

An extensive neuropsychological battery was selected to assess seven neurocognitive domains (see Table 2.2). In addition, decision making was assessed with the GDT. Psychosocial factors were assessed with the MOS-HIV (Wu, et al., 1997) and the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983). Patients' self-rated involvement in and perceived riskiness of everyday situations was also tested (i.e., Domain Specific Risk Taking – DOSPERT; Blais & Weber, 2006). Of all tests administered, only the GDT and DOSPERT have not previously been used in an HIV+ population.

Table 2.2 Neuropsychological and Questionnaire Measures

Function/Domain	**Test**
Decision making	Game of Dice Task (GDT)
Pre-morbid IQ	Shipley Institute of Living – Part A
Processing Speed, Attention	WAIS-III Digit Span forward Paced Auditory Serial Additions Test (PASAT) – 3 second Symbol-Digit Modalities Test (SDMT) D-KEFS Trail Making Test -2

Function/Domain	Test
	D-KEFS Color-Word-Interference Test, Reading/Color Naming Trials
Working Memory	WAIS-III Digit Span backward
Verbal Memory	Verbal Selective Reminding Task (VSRT)
Executive Functions	D-KEFS Trail Making Test-4 Wisconsin Card Sorting Test –64 card version D-KEFS Color-Word-Interference Task, Interference Trial
Verbal Fluency	Controlled Word Association Task (COWAT)
Motor Skills	9-Hole Pegboard
Visuo-spatial Memory	Rey-Osterrieth Complex Figure Test (ROCF)
Mood	Hospital Anxiety & Depression Scale (HADS)
Functional Assessment	Medical Outcomes Study HIV Health Survey (MOS-HIV)
Risk Taking and Perception	Domain-Specific Risk-Taking (DOSPERT)

2.2.1. Paced Auditory Serial Additions Test (PASAT)

The PASAT is one of the most robust neuropsychological tests to detect neurocognitive impairment in information processing speed and attention (Gronwall, 1977). Only the 3-second version was used here. In the task, a voice recording says a single digit, 1 through 9, at a rate of one digit per every three seconds. Participants must mentally add each two consecutive numbers and verbally provide an answer. If a number is missed, participants are asked to continue with the task (example, see Figure 2.1).

Presentation	9+1	3	5	2	6	4	9	7	1	4
Correct response	10__	4 __	8 __	7 __	8 __	10__	13__	16__	8 __	5 __

Figure 2.1. Example item from PASAT; top line shows the numbers heard on the audio recording and bottom line displays correct response for tester's scoring.

The PASAT takes about 5-8 minutes to complete, including instruction time and practice. The measure of interest is the number of correct responses over 60 test trials (Gronwall, 1977).

2.2.2. Symbol-Digit Modalities Test (SDMT)

The Symbol-Digit Modalities Test (SDMT) assesses speed of information processing and attention. Participants are provided a written key with non-sense symbols and a corresponding number between one and nine (see Figure 2.2). A total of 120 symbols are given in a random order and participants must write the number corresponding to each digit, in sequential order (Smith, 1982). The score of interest is the number of correct responses given in 90 seconds. The SDMT takes less than 5 minutes to administer.

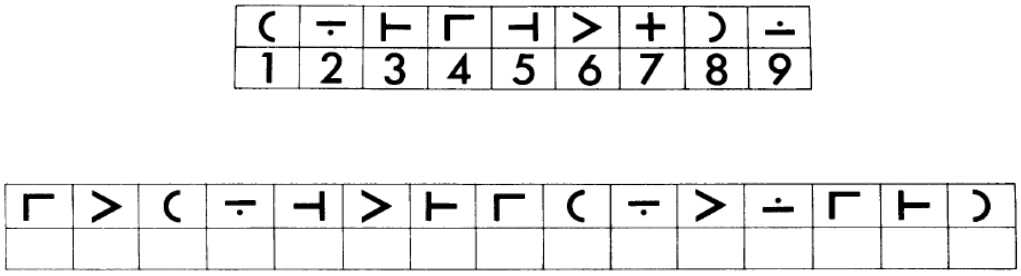

Figure 2.2. Task key and example row of the Symbol-Digit Modalities Test.

2.2.3. WAIS-III Digit Span - Forward & Backward

The Digit Span task in this study was taken from the Wechsler Adult Intelligence Scale-III (Wechsler, 1997). This task measures verbal short-term memory (forward span) and working memory (backward span). In both versions, the experimenter reads sequences of digits in increasing length to the participant, who is then asked to verbally repeat the digit sequence in either the forward or

backward direction. Two digit sequences of the same length are presented and if the participant correctly repeats at least one of the two, the next presented sequence is increased by one digit, to a maximum of nine digits (forward span) or eight digits (backward span). This study used the total number of completed digit span (forward) and digit span (backward) trials (Wechsler, 1997).

2.2.4. D-KEFS Trail Making Tests

This study used the Delis–Kaplan Executive Function System (D-KEFS) Trail Making Tests (TMT)-2 and -4 (Delis, Kaplan, & Kramer, 2001), similar to former Trail Making Tests (*Army Individual Test Battery*, 1944). A timed pencil and paper task, administration of both tasks takes approximately 5 minutes. The TMTs measure attention, motor skills and visual search; TMT-4 additionally measures executive function. TMT-2 requires the participant to connect numbered circles in consecutive order (i.e., 1-2-3-4-5...up to 16). TMT-4 is a similar task, but requires participants to connect alternating numbers and letters in consecutive order (i.e., 1-A-2-B-3-C... up to 16-P). Both versions of the task provide a short, half-page example. The test trials occupy two letter-sized pages. Participants are interrupted if they make mistakes (e.g., fail to connect the next number or letter in TMT-2; or fail to alternate correctly between numbers and letters in TMT-4). Time to complete each task (*TMT-2 time* and *TMT-4 time*) and the number of errors in each task (*TMT-2 errors* and *TMT-4 errors*) are the measures of interest in this thesis. Note that different types of possible errors (self-corrected, uncorrected, etc.) can be calculated separately, but were combined in this study.

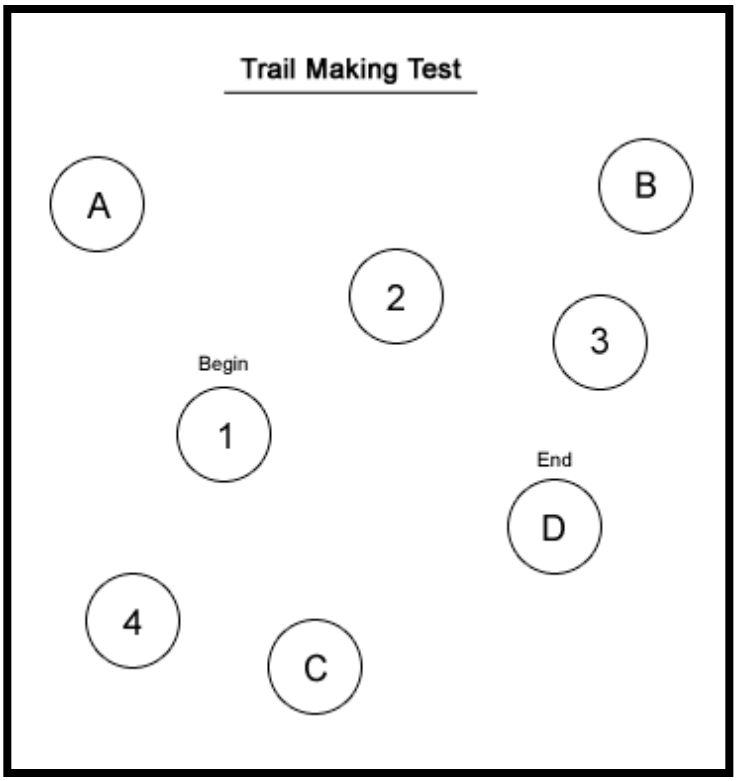

Figure 2.3. Example illustrating a practice sample in the TMT-4.

2.2.5. D-KEFS Colour-Word Interference Test

The Colour-Word Interference Test in this study was also taken from the D-KEFS (Delis, et al., 2001). This test was administered to all but one participant who reported colour blindness. The task involves three conditions: 'Colour-Naming', 'Word-Reading' and 'Interference'. In the 'Colour-Naming' condition, participants must name the colour of small quarter-inch, green, red or blue boxes on a letter-sized cue card. In the 'Word-Reading' condition, colour words are provided and printed in black. Words must be read aloud. The 'Interference' condition combines competing font colour and text (Figure 2.4), and asks the participant to name the colour of each word while suppressing reading the text. 'Colour-Naming' and 'Word-Reading' measure speed of information processing,

while the 'Interference' condition measures executive functioning. In this task, participants are not corrected if they make a mistake. Time to complete each condition (*D-KEFS colour-naming time*, *D-KEFS word-reading time* and *D-KEFS interference time*) and number of errors made (*D-KEFS colour-naming errors*, *D-KEFS word-reading errors* and *D-KEFS interference errors*) are the measures of interest here (Delis, et al., 2001). As in the TMT, different types of errors were combined in this study.

Figure 2.4. Example items from the interference condition on the D-KEFS Colour-Word Interference Task.

2.2.6. Verbal Selective Reminding Task (VSRT)

The VSRT is a verbal memory task; a shortened 6-trial version was administered in this study (Hannay & Levin, 1985). The tester reads a list of 12 common nouns and participants are asked to verbally recall these words; participants are then reminded of any words they have missed but prompted to repeat the entire list, including also the words they had recalled initially. This process is repeated until either the full list of 12 words is recalled twice, or to a maximum of six attempts. A 30-minute delayed recall is also included. Measures of interest included *VSRT total recall*, *VSRT intrusions* and *VSRT delayed recall*. Total recall is the sum of correctly recalled word over the first six trials. Intrusions

refer to the number of extra-list words produced over the six trials. Delayed recall is the number of correctly recalled words at the 30-minute delay.

2.2.7. Rey-Osterrieth Complex Figure Test (ROCF)

The Rey-Osterrieth Complex Figure Test measures visuospatial construction and memory (version from Meyers & Meyers [1995]; original: Osterrieth [1944]). The participant is presented with a complex line drawing (see Figure 2.5) and is required to copy the drawing by pencil/pen on a blank sheet of paper.

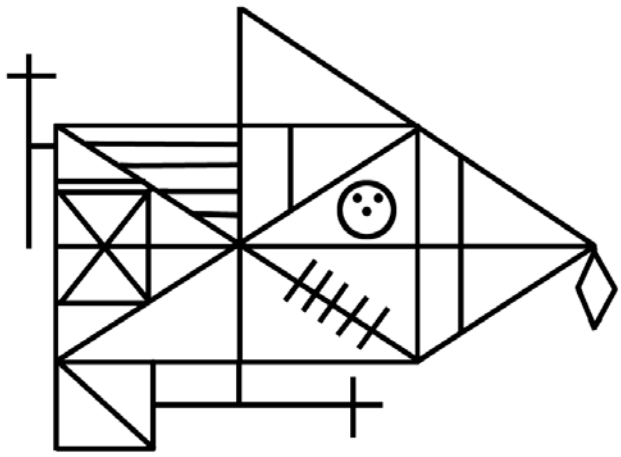

Figure 2.5. Rey-Osterrieth Complex Figure Test.

A minimum exposure of two and maximum exposure of five minutes is given for copying the figure. Rulers or erasers are not permitted. Two surprise recall trials are conducted three minutes and 30 minutes after the initial copy task, for which the participant is to re-draw the figure from memory. Each iteration is scored based on specific criteria for accuracy and completeness, with a maximum score of 36 points (scoring was conducted according to Meyers & Meyers, 1995).

The *ROCF copy* score, *ROCF immediate* recall score after three minutes and *ROCF delayed* recall score after 30 minutes were used in this study.

2.2.8. Wisconsin Card Sort Task (WCST) - 64 card version

The WCST is used to assess executive functioning, specifically cognitive flexibility and set-shifting (Kongs, 2000). The shortened 64-card version was administered using a physical deck of cards. Participants are asked to match each one of the 64 individually presented cards to one of four key cards (see example in Figure 2.6). Cards can be matched based on their number, colour and/or shape.

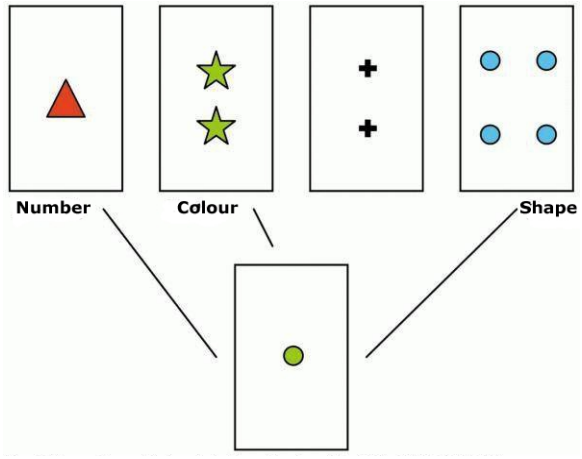

Figure 2.6. Example of the Wisconsin Card Sorting Test (WCST). On top are the four key cards which each cue card must be matched to. The bottom card (green dot) can be sorted into either the category number (one red triangle), colour (two green stars) or shape (four blue dots).

Matching criteria are not explained and the sorting rules are changed unannounced based on a predetermined pattern (e.g., successfully matching ten consecutive cards based on colour, followed by successfully matching ten cards based on number, etc.). Participants are given verbal feedback ("correct"/

"incorrect") after each trial. The WCST is a widely used measure of executive function from which many scores can be derived. The analysis here included the number of correct sorts out of 64 (*WCST total correct*), the number of errors that a participant continued to make despite having received negative feedback about their incorrect sorting rule (*WCST perseverative errors)* and the number of other, non-perseverative sorting errors (*WCST non-perseverative errors).*

2.2.9. Controlled Oral Word Association Test (COWAT)

The Controlled Oral Word Association Test (Borkowski, Benton, & Spreen, 1967) is a verbal fluency task to assess language and executive functions. Participants are asked to produce, in 60 seconds, as many words as possible that start with a specific letter. Three trials were conducted asking for words starting with letters F, A, and S. Naming rules, which are explained to the participant in the beginning, exclude proper names (e.g., Billy, Boston) and re-using the same word with various endings (e.g., go, going, goes). The total number of correct words produced over all three letter trials was used in this study (*COWAT-total)* as well as the number of repeated words (*COWAT-perseverations).*

2.2.10. Nine-hole Pegboard

The Nine-hole pegboard (Mathiowetz, Volland, Kashman, & Weber, 1985) is used to assess manual dexterity and motor speed (see Figure 2.7.). In this timed task, participants are asked to pick up one peg at a time from the holding area and place it in any hole until all nine holes are filled, as quickly as possible. The participant then immediately begins removing each peg and returns it to the holding area. This is done first with the dominant hand, then with the non-

dominant hand. The time to insert and remove all nine pegs with each hand was the measure of interest in the current study (*9-hole pegboard, dominant hand, 9-hole pegboard, non-dominant hand).*

Figure 2.7. The 9-Hole Pegboard Test (with cover in the background).

2.2.11. Shipley Institute of Living Scales – Part A (Vocabulary)

The Shipley Institute of Living Scales – vocabulary subtest is a forty item paper-and-pencil test of vocabulary, and was used as an approximate measure of pre-morbid intelligence. In the task, all items are presented at once on the same sheet of paper, and the order of completion does not matter. The participant is given one target word (e.g. LARGE) and must select one out of four choice alternatives that has the most similar meaning to the target word (e.g. red, big, silent, wet). Presented target words are increasingly unusual and therefore, understanding of the word meanings is thought to reflect pre-morbid exposure/education levels. The measure of interest is the number of correct answers from which a pre-morbid IQ estimate was derived (Zachary, et al., 1985).

2.2.12. Game of Dice Task (GDT)

The GDT is used to test decision making under risk (Brand, et al., 2005b). As described in section 1.2.2, the task is computer-based and uses visual and auditory feedback. Prior to administration there are extensive written instructions on how the task works and what is being asked of the participant. In this study, all participants were walked through the instruction screens verbally by the tester. The task is self-paced and takes roughly 8 minutes to complete (see Figure 2.8 for the task screen at the beginning of the GDT).

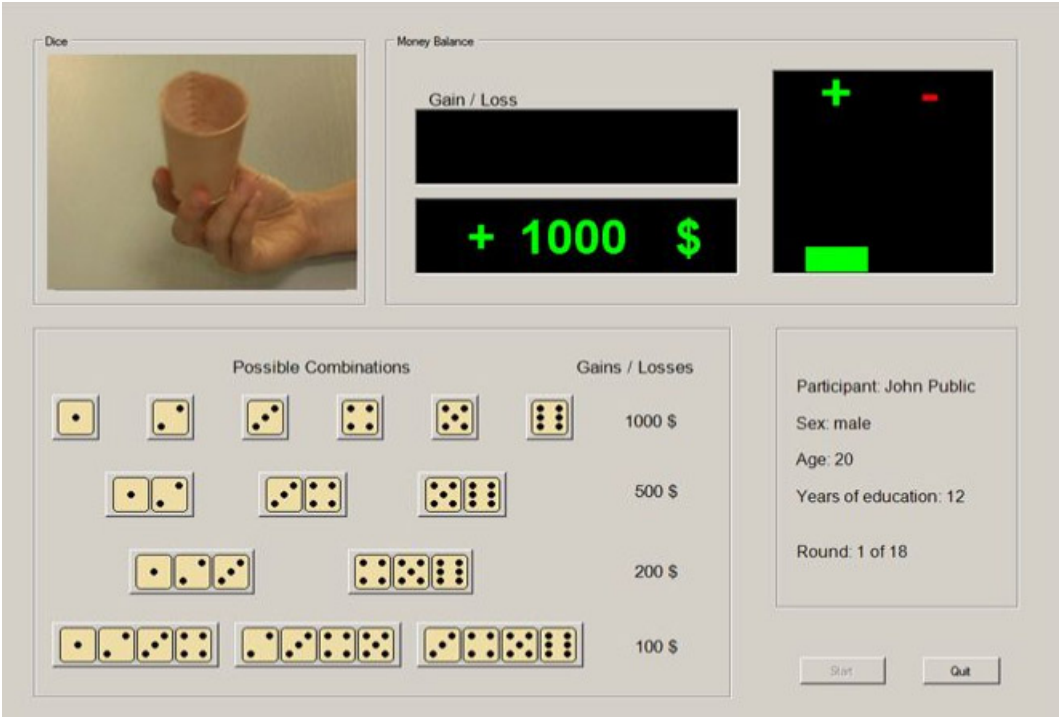

Figure 2.8. Screenshot of the GDT at the starting point of the game.

Participants are told that they are to win as much fictitious money as possible and lose as little money as possible. Participants begin with a balance of $1,000 and are told they can continue to play even if in debt. At the beginning of

each of 18 rounds of play, participants first select one of 14 different choice options. Their selection is a bet on the possible outcome of a single die rolled in a cup, displayed as a video clip on the top left corner of the screen (see Figure 2.8). Possible bets range across four levels of risk based on the number of dice included in any one selection: The more dice included in a choice option, the greater the chances of winning/lesser the chances of losing, with the corresponding money amount of a possible gain/loss staggered across risk levels. For example, choosing a single number bet has a 1/6 (17%) chance of winning, 5/6 (83%) chance of losing and is associated with a possible win/loss of $1,000. Choosing a four-number combination has a 4/6 (67%) chance of winning, a 2/6 (33%) chance of losing and is associated with a possible win/loss of $100. Risky choices are single- and two-number bets, as their winning probability is less than 50%, safe chances are 3- and 4-number combinations with winning probabilities of 50% or more. After making a selection, the video clip shows the outcome of the single die roll. If the number on that single die matches any one of the dice in the selection made, the participant is awarded the corresponding funds; if it does not match, the funds are lost. The screen display provides immediate visual and auditory feedback about the outcome of each bet based on a win or loss.

The GDT can be used to evaluate the use of feedback, strategies and patterns or changes in the decision process. The primary measure of interest derived from the task is the *net-score*. The GDT net-score is established by subtracting the number of risky choices (bets on 1-number or 2-number combinations) from safe choices (bets on 3-number combinations or 4-number

combinations). In addition, the total amount of money won (*GDT sum*) at the end of the game is calculated. Also examined are the total *number of shifts;* this score is computed by counting how often a participant changes their choice strategy between risky and safe choices. For example, making the following consecutive bets: (A) 2-1-1-1-2-2 or (B) 4-4-3-3-4-3, equals no shifting between risk levels. In case (A), the participant consistently stays within risky choices, in case (B), the participant stays within safe choices. Conversely, a 4#2-1#3-4#1 pattern would equal three shifts (represented by # here).

2.2.13. Medical Outcomes Study HIV Health Survey (MOS-HIV)

The Medical Outcomes Study HIV Health Survey (MOS-HIV) was first developed in 1987 specifically for use in HIV/AIDS clinical trials (Wu, et al., 1991). The measure is designed to capture subjectively perceived health and quality of life including aspects of pain, social functioning, mental health, cognitive capabilities, energy, and physical capabilities. The 35 items require responses on severity or degree of impact (see Figure 2.9 for an example item).

4. The following questions are about activities you might do during a typical day. Does your **health now limit you** in these activities? If so, how much?

(Check **one** box on **each** line.)		**YES, limited a lot**	**YES, limited a little**	**NO, not limited**
a.	The kinds or amounts of **vigorous** activities you can do, like lifting heavy objects, running or participating in strenuous sports.	1 ☐	2 ☐	3 ☐
b.	The kinds or amounts of **moderate** activities you can do, like moving a table, carrying groceries or bowling.	1 ☐	2 ☐	3 ☐
c.	Walking uphill or climbing (a few flights of stairs).	1 ☐	2 ☐	3 ☐
d.	Bending, lifting or stooping.	1 ☐	2 ☐	3 ☐
e.	Walking one block.	1 ☐	2 ☐	3 ☐
f.	Eating, dressing, bathing or using the toilet.	1 ☐	2 ☐	3 ☐

Figure 2.9. Example item from MOS-HIV.

Typically administered as a pencil and paper task, the MOS-HIV can also be conducted verbally. Summary scores for physical (*MOS-HIV physical summary*) and mental health (*MOS-HIV mental summary*) were used in the current study, although a finer-grained breakdown into subscales is also possible (Wu, et al., 1997). Internal consistency for the physical health summary score ranged from .90 to .92 and for the mental health summary score ranged from .91 to .94 across previous patient samples (Wu, et al., 1997).

2.2.14. Domain-Specific Risk-Taking (DOSPERT)

The Domain-Specific Risk-Taking (DOSPERT; Blais & Weber, 2006) scale measures risk taking and risk perception. The 30-item questionnaire uses brief hypothetical situations rated on a seven point scale (see Figure 2.10 for an

example of the risk taking portion of the scale, DOSPERT-A). Situations include financial, social, health and safety, recreational and ethical decision scenarios.

Domain-Specific Risk-Taking (Adult) Scale – **Risk Taking**

For each of the following statements, please indicate the **likelihood** that you would engage in the described activity or behavior if you were to find yourself in that situation.

Provide a rating from *Extremely Unlikely* to *Extremely Likely*, using the following scale:

1	2	3	4	5	6	7
Extremely Unlikely	Moderately Unlikely	Somewhat Unlikely	Not Sure	Somewhat Likely	Moderately Likely	Extremely Likely

STATEMENT	YOUR ANSWER
1. Admitting that your tastes are different from those of a friend.	
2. Going camping in the wilderness.	
3. Betting a day's income at the horse races.	
4. Investing 10% of your annual income in a moderate growth mutual fund.	

Figure 2.10. Sample of DOSPERT-A; instructions, scale and four example items are displayed.

The same 30 items are presented twice. First, the participant is asked to evaluate the degree to which he/she is likely to engage in the decision scenario (i.e. risk taking, DOSPERT-A) and secondly, the participants is asked to evaluate the degree of perceived risk associated with each scenario (i.e. risk perception, DOSPERT-B). Each of the 30 items is associated to one of five domains noted above. Subscales for each domain can be computed, although for this study only overall scores for the likeliness to engage in risky scenarios (DOSPERT-A) and for their perceived risk (DOSPERT-B) were used. Internal consistency (Cronbach's alpha) for the 30-item, English version administered were between .71 to .86 for DOSPERT-A and between .74 to .83 for DOSPERT-B (Blais & Weber, 2006).

2.2.15. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) is a 14-item questionnaire developed to assess mood of non-psychiatric hospital outpatients. Half of the items target depression and the other half target anxiety. For each question, participants rate the item for the degree of endorsement on a scale of 0 to 3. The task takes a few minutes to complete and does not include questions that can be endorsed based on physical symptoms alone, unrelated to mood. The task uses reverse scoring for approximately half of the questions and sum scores for both depression and anxiety are produced based on the severity of items endorsed. The HADS is a screening tool only, and may not definitively differentiate anxiety from depression (e.g., Cosco, Doyle, Ward, & McGee, 2012). Nevertheless, this screening was included as an estimate for global current mood state, as lowered mood is common in HIV (Carrico, et al., 2007; Penzak, Reddy, & Grimsley, 2000) and plays a role in cognitive functions in HIV (Castellon, et al., 2006; Sadek, Vigil, Grant, & Heaton, 2007). In addition, depression can reduce decision making performance regardless of HIV status (Cella, Dymond, & Cooper, 2010) as well as in HIV patients with comorbid depression (Thames et al. 2012).

2.3. Procedure

After participants were determined eligible for participation through our screening form, a two-hour test time was scheduled. For patients, testing was often performed on the same day. All participants were compensated nominally for their time to participate in the study ($30 for expenses). The test battery took

approximately 2 hours to complete, with breaks offered throughout the session. Tasks were administered in the same order for all participants (see Table 2.3).

Table 2.3 Testing Protocol

Test	Time (minutes)
Setup and consent	5
1. Symbol-Digit Modalities Test	3
2. Verbal Selective Reminding Task (immediate)	12
3. Game of Dice Task	8
4. Paced Auditory Serial Addition Test (PASAT)	5
5. 9-Hole Pegboard	3
6. Tower of Hanoi*	6
7. Verbal Selective Reminding Task (SRT) (delay)	2
BREAK	
8. Wisconsin Card Sorting Test (WCST) 64 card version	10
9. Rey Complex Figure Test (ROCF) (copy)	5
10. Digit Spans	2
11. Rey-Osterrieth Complex Figure Test (ROCF) (3 minute delay)	3
11. Controlled Word Association Task (COWAT)	4
12. Shipley Institute of Living – Part I (verbal)	10
13. D-KEFS Colour-Word Interference Test	8
14. D-KEFS Trail Making Test-2	5
15. D-KEFS Trail Making Test-4	5
16. Rey-Osterrieth Complex Figure Test (ROCF) (30-minute delay)	5
Questionnaires	
17. Domain-Specific Risk-Taking (DOSPERT)	10
18. Hospital Anxiety and Depression Scale (HADS)**	5
19. Medical Outcomes Study HIV Health Survey (MOS-HIV)**	10
Total Time	**120**

*Only completed by controls in the context of a separate study; scores are not included in thesis
**Only completed by HIV-patients

For HIV-patients, a chart review was conducted post-testing to collect viral load, current and nadir CD4+ T-cell count, and length of HIV-infection.

2.4. Statistical Analyses

Data were tested for normality using the one-sample Kolmogorov-Smirnov test. For between-group comparisons, independent t-tests on means were

performed for normally distributed variables, or Mann-Whitney tests on medians for non-normal variables. Correlations were conducted with Pearson or Spearman rank correlations, respectively. Further fine-grained analyses of the GDT data are detailed in the results section. These included partial correlations controlling for intelligence or age, and repeated measures analysis of variance to compare frequencies of choices from the four risk levels between groups.

The current study included a large number of test instruments and scores within tests. To account for this high number, but retain meaningful information about group differences and correlations within groups, results were Bonferroni-corrected by the number of scores used within each test but not across tests. Adjusted alpha levels per test instrument are listed in Table A.2. in the Appendix. Results are presented both uncorrected, and Bonferroni-corrected. Multivariate analysis methods would reduce the number of these comparisons; however these would require larger sample sizes and were not further attempted here. It is acknowledged that summarising the cognitive data into composite scores of neuropsychological performance is another option to reduce the number of comparisons that was not attempted here. However, the nature of this study was to explore specific relationships between decision making in the GDT and aspects of executive functions. Furthermore, the number of executive function tests was considerably higher than tests assessing other cognitive domains. Thus, to retain detailed information about specific GDT –executive function relationships, data were not further comprised into composite neuropsychological scores here and statistical significance thresholds were adjusted within each test only.

3. RESULTS

The results section is structured as follows. After a descriptive characterization of the participants, group differences in neuropsychological performance are first reported to provide an overview on the patients' general cognitive status and to address hypothesis one. Secondly, to address hypothesis two, group differences in GDT performance are reported, including several analyses. The last section provides correlations between the GDT and HIV-specific variables as well as cognitive parameters to address hypothesis three.

3.1. Participant characteristics

As can be seen in Table 3.1., although controls had a slightly higher pre-morbid IQ estimate than patients, this difference was not significant and neither were differences in any of the other demographic characteristics. Of the patients, 17/20 individuals had undetectable viral load. Nadir CD4+ T-cell count was unavailable for two patients. Four of the twenty patients (20%) were classified as "symptomatic", on the basis of reported cognitive problems (self- or caregiver-report). Clinical assignment of HAND was based on prior neuropsychological testing, self- and caregiver-report of cognitive problems, and MRI (excluding patients with MRI findings indicative of other CNS-related pathology, such as head trauma). HAND was present in 6/20 (30%) of the patients. A total of 15 patients (75%) were classified as having once progressed to AIDS. This was defined based on the US guidelines (Ref?), as a CD4+ T-cell count that had dropped below 200cells/mm^3 at some point during the course of the illness. Patients' current antiretroviral medication regime is described in more detail in

Table A.4. in the Appendix. All but two patients were receiving ART. These two patients had high CD4+ T-cell counts (806 and 1,150cells/mm^3) and either had undetectable or very low (260 copies/mL) viral loads, respectively.

Table 3.1 Participant Characteristics

	HIV + (n=20) Mean (SD)	**Healthy Controls (n=20) Mean (SD)**	**Statistical Test**
Sex (male/female)	15/5	11/9	χ^2=1.758, p=0.185
Age	48.2 (9.9)	47.2 (10.1)	t(38)=0.464, p=0.646
Pre-morbid IQ*	103.5 (14.5)	110.7 (10.0)	t(38)=-1.807, p=0.079
Education	14.0 (2.8)	14.9 (2.0)	t(38)=-1.564, p=0.126
Years with HIV	10.65 (8.01)	-	-
Viral load (copies/ml)	3 detectable (copies/ml): 537 800,000 260	-	-
CD4+ T-cell count (per mm^3)	415.90 (281.23)	-	-
CD4+ T-cell count nadir (per mm^3)**	156.33 (209.38)	-	-
Symptomatic	4 (20%)	-	-
HAND	6 (30%)	-	-
AIDS***	15 (75%)		

*Determined by performance on the Shipley Institute of Living – Part A (Zachary, Paulson, & Gorsuch, 1985); see section 2.2.11 for a description. ** Available for 18 patients. ***based on historical CD4+ T-cell counts/per mm^3 below 200

3.2. Group Difference in Neuropsychological Battery

As detailed in Table 3.2, the neuropsychological battery revealed impairments in the HIV+ group compared to the control population. Significant differences were reported in attention and processing speed, executive functions

and working memory, language (verbal fluency), and motor speed. While verbal learning was impaired on immediate recall, retention/memory was unimpaired, as was visual memory. The control group in this study performed within the normal range based on published norms for the employed neuropsychological tests (see Table A.4. in the Appendix). These results are similar to previous neuropsychological findings in HIV (see section 1.1.4: Berger & Arendt, 2000; Cohen, 2009; Grant, 2008; Kieburtz, et al., 1996; Steinbrink, et al., 2013) and confirm hypothesis one.

Table 3.2. **Neuropsychological Test Results**[1]

Domain Test score	**HIV+ Patients Mean (SD)**	**Healthy Controls Mean (SD)**	**Test statistic/ significance**
Attention/Information Processing Speed			
Symbol-Digit	45.25 (11.62)	56.05 (11.98)	t[38]= -2.89*
PASAT	39.2 (12.26)	51.3 (8.77)	t[38]=-3.59*
D-KEFS TMT-2 time[1]	Md: 47 (Rg: 25-66)	Md: 31 (Rg: 17-198)	Z[34]= -2.81*
D-KEFS Colour Naming time	36.41 (13.19)	29.18 (6.06)	t[34]=2.11†
D-KEFS Word Reading time[1]	Md: 24.5 (Rg: 18-82)	Md: 21 (Rg: 14.6-28)	Z[35]= -2.57*
Digit span forward	9.55 (2.63)	11.65 (1.79)	t[38]=-2.96*
Memory			
SRT immediate recall	46.11 (10.79)	54.1 (8.12)	t[37]=-2.62*
SRT delayed recall	7.37 (2.73)	8.15 (2.41)	t[37]=-0.95
ROCF immediate recall	17.71 (6.71)	20.26 (7.79)	t[32]=-1.03
ROCF delayed recall	18.21 (6.25)	19.85 (7.93)	t[32]=-0.67
Executive Functions			
WCST correct sorts	47.4 (6.38)	51.9 (4.23)	t[38]=-2.63*
WCST perseverative errors	10.75 (5.23)	6 (2.27)	t[38]=3.52*
WCST non-perseverative errors[1]	Md: 6 (Rg: 2-21)	Md: 5 (Rg: 2-13)	Z[38]= -0.72
COWAT perseverations	2.4 (2.68)	2.65 (2.41)	t[38]=-0.31
SRT intrusions[1]	Md: 1 (Rg: 0-4)	Md: 0 (Rg: 0-6)	Z[37]= -1.96
D-KEFS Inhibition time	69.64 (31.71)	51.29 (11.88)	t[34]=2.3†
D-KEFS Color Naming errors[1]	Md: 0 (Rg: 0-3)	Md: 0 (Rg: 0-2)	Z[34]= -1.4
D-KEFS Word Reading errors[1]	Md: 0 (Rg: 0)	Md: 0 (Rg: 0-1)	Z[35]= -1.74
D-KEFS Inhibition errors[1]	Md: 1.5 (Rg: 0-12)	Md: 0 (Rg: 0-3)	Z[34]= -2.52*

Domain Test score	**HIV+ Patients Mean (SD)**	**Healthy Controls Mean (SD)**	**Test statistic/ significance**
D-KEFS TMT 2 errors[1]	Md: 0 (Rg: 0)	Md: 0 (Rg: 0-1)	Z[34]= -0.95
D-KEFS TMT 4 time	95.94 (34.68)	68.48 (26.43)	t[34]=2.69*
D-KEFS TMT 4 errors[1]	Md: 0 (Rg: 0-4)	Md: 0 (Rg: 0-2)	Z[34]= -0.33
Digit span backwards	6.05 (2.31)	7.74 (2)	t[37]=-2.44*
Visuo-spatial ability			
ROCF copy[1]	Md: 32 (Rg: 24-36)	Md: 35 (Rg: 27-36)	Z[32]= -1.26
Language			
COWAT	37.9 (13.98)	47.35 (10.64)	t[38]=-2.41*
Motor Speed			
Pegboard dominant hand	24.2 (5.24)	19.98 (3.19)	t[37]=3.02*
Pegboard non-dominant hand	25.05 (6.89)	21.16 (3.37)	t[37]=2.22†

[1] Scores are means (standard deviations) unless otherwise stated. *: $p < .05$ after Bonferroni-correction for the number of variables tested within each test instrument; †: $p < .05$, uncorrected; [1]: Mann-Whitney U-Test; Md: Median; Rg: Range

Neuropsychological test scores were not further compared between patient subgroups with/without HAND, symptomatic status, or AIDS due to very small sub-group sample sizes (N= 6 vs. 14; N= 4 vs. 16; or N= 15 vs. 5, respectively). Furthermore, as the sampling was not optimized to assess such differences, substantial demographic differences between sub-samples became apparent. For example, patients with HAND were about 9 years older than patients without HAND (patients with HAND: M= 54.15 ± 7.3 years; patients without HAND: M= 45.77 ± 10 years) and had a 10-point higher estimated pre-morbid IQ (patients with HAND: M= 110.5 ± 16.21; patients without HAND: M= 100.54 ± 13.21). These differences were even more pronounced when comparing the four symptomatic patients against the sixteen non-symptomatic patients, considering age (non-symptomatic patients: M=45.8 ± 9.39 years; symptomatic patients: M = 58.19 ± 4.13 years) and estimated pre-morbid IQ (non-symptomatic patients: M=

99.34 ± 13.14; symptomatic patients: M= 120.25 ± 1.94 years). Thus, apart from the differences in sub-groups' sizes, substantial demographic differences permitted valid conclusions about the impact of disease status on cognitive performance here. Therefore, such analyses were not further pursued.

Nevertheless, to further characterise the entire patient sample, questionnaire results are outlined here. To recapitulate, HIV+ patients completed three questionnaires, the HADS, MOS and DOSPERT; the healthy controls also completed the DOSPERT but did not complete the HADS or MOS. Results are detailed in Table 3.3.

Table 3.3 Questionnaire Results

Domain Test score	**HIV+ Patients Mean (SD)**	**Healthy Controls Mean (SD)**	**Test statistic/ significance**
HADS – Anxiety	9.75 (5.83)		
HADS – Depression	5.7 (5.11)		
MOS – Physical (T-score)	43.7 (13.95)		
MOS – Mental (T-score)	43.2 (16.34)		
DOSPERT – A	94.71 (25.91)	94.42 (17.72)	t[34]=.04
DOSPERT – B	144.82 (25.33)	137.42 (18.26)	t[34]=1.01

HADS scores are classified as indicating either mild (8-10 points), moderate (11-15 points) or severe (16+ points) levels of depression/anxiety (Zigmond & Snaith, 1983). Scores below 8 reflect no depression/anxiety. The HIV+ patients in this study reported no elevated levels of depression but showed mild levels of anxiety in the HADS.

The MOS-HIV (Wu, et al., 1991) showed slightly elevated levels in both physical and mental health-related problems in the patient sample. Patients numerically scored below published norms for controls in both summary scales of

the MOS (M=50, SD=10; (Wu, et al., 1991). However, their level of impairment was mild, as evidenced by the T-scores in Table 3.3. Expressed in standard deviations, the MOS-Physical Health summary score of the HIV+ sample here was 0.63 standard deviations below norm scores of controls. The MOS-Mental Health summary score was 0.68 standard deviations below the norm controls' mean. Thus, patients in the current study reported slightly but not substantially elevated concerns about their physical and mental health status.

The DOSPERT showed no significant difference between the healthy control and HIV+ group. Both groups showed similar perceptions of risk and propensity to engage in risky behaviours.

3.3. Group Difference in Decision Making

In comparing the HIV+ and control groups on the primary measure of interest for decision making (*net-score*), a significant difference in performance between the two groups ($t[38]= -2.51$, $p<0.05$; Fig. 3.1) was detected. Over 18 trials, the HIV+ group had significantly lower performance scores (M= 4.3, SD= 10.59) than the healthy controls (M=11.6, SD= 7.56), Cohen's *d*=.79 (indicating a moderate to large effect size of this difference). A post-hoc power calculation indicated a statistical power of 0.81 with a sample size of 20 patients/controls (Rosner, 2011).

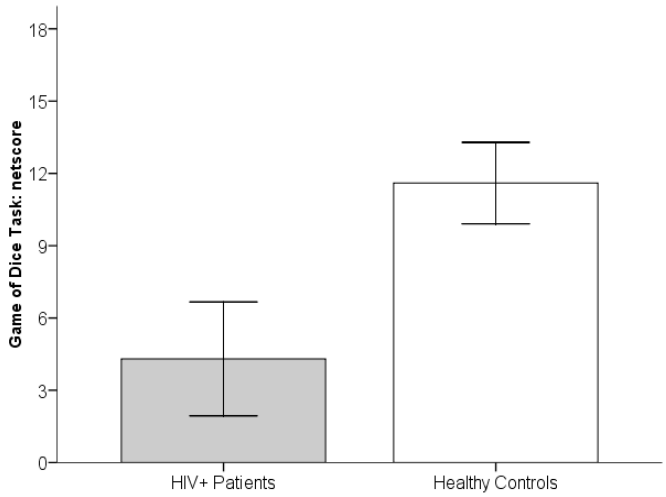

Figure 3.1. GDT net-scores in the HIV+ and healthy control group. Patients differed significantly from controls. Error bars are standard errors of the mean.

Of note, the GDT net-score did not differ between subgroups of patients with and without HAND (HAND: M= 4.17, SD= 10.11; no-HAND: M= 4.5, SD= 11.94, ($t[18]= -0.07$, $p>0.1$). Since HAND subgroups' GDT net-scores were almost identical, no further analyses involving HAND status and GDT were performed.

Figure 3.2 illustrates the distribution of participants' net-score across the continuum of -18 (minimum) and +18 (maximum) within each of the two groups. The majority of healthy controls reached positive GDT net-scores. Indeed, 75% of healthy controls (N=15) had a GDT net-score of 10 or above. In contrast, the HIV+ patients' distribution of net-scores was more varied, spanning the entire range of possible GDT outcomes (i.e., -18 to +18).

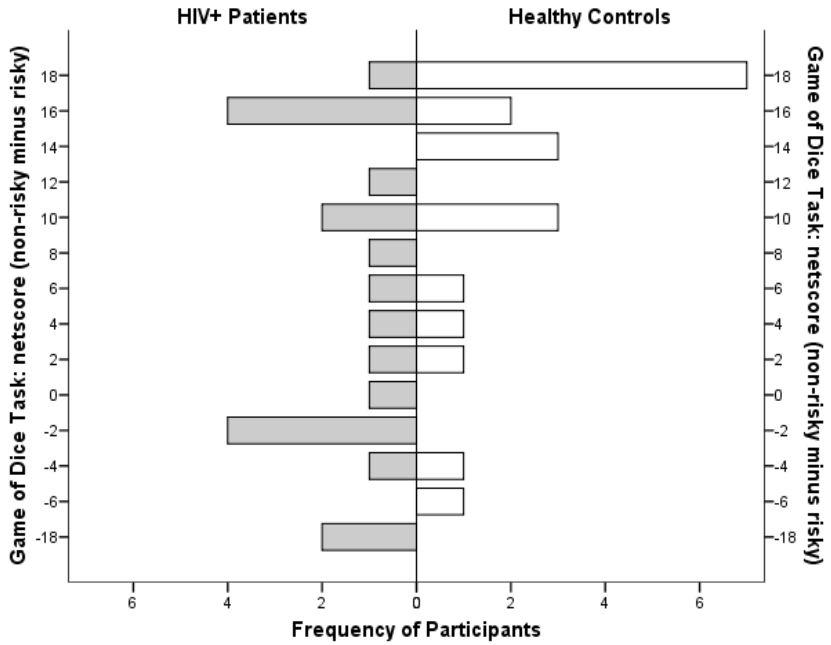

Figure 3.2. Frequency of participants by GDT net-score and group.

The HIV+ group also earned significantly less money in the GDT (sum after 18 trials: M= $ -2,195, SD= $2,891]) than the controls (M= $ -305, SD= $1,889.72, t[38]= -2.45, p=.019; see Figure. 3.3). Taken together, this leads to a confirmation of hypothesis two: patients with HIV+ performed worse than healthy controls in the GDT.

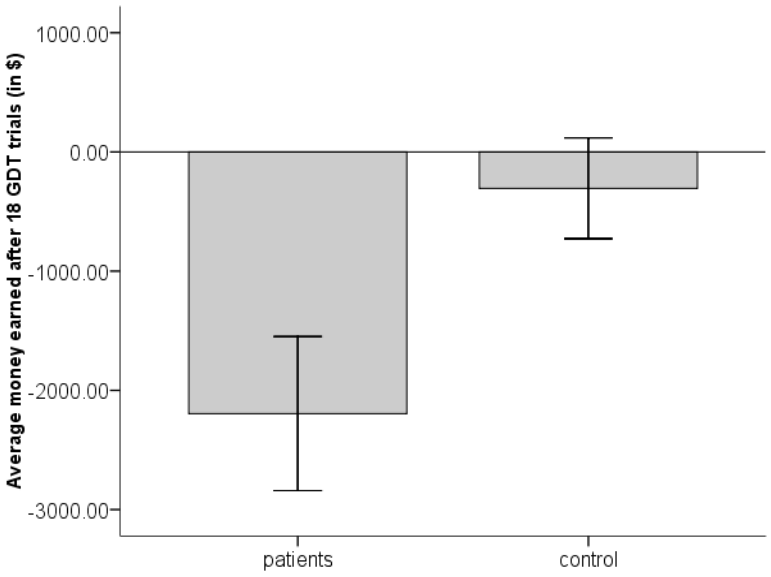

Figure 3.3. HIV+ patients earned significantly less money than the healthy controls after 18 GDT trials. Error bars are standard errors of the mean.

3.4. Group Difference in Decision Making, Controlling for IQ

Notably, the HIV+ group showed a wide range of cognitive impairment and also had a (non-significantly) lower level of pre-morbid intelligence. Therefore, GDT performance might have been confounded by HIV-patients' marginally lower IQ. There are several equivalent ways to control for this potential confound with a two-group design (Bay & Hakstianz, 1972). A partial point-biserial correlation between GDT net-score and group (dummy-coded: 0 = controls, 1 = patients) was conducted, controlling for pre-morbid IQ. The point-biserial correlation between GDT net-score and group amounted to: $r_{pb}[39]= 0.377$, $p = 0.016$, which is equivalent to the result of the t-test (see above). The partial correlation controlling for IQ was $r_{pb\text{-}part}[37]= 0.337$, $p = 0.019$. Thus, controlling

for IQ did not substantially influence the result that HIV+ participants underperformed in the GDT compared to controls.

3.5. GDT Response Patterns Over Risk Levels

The pattern of responding in the GDT was further analyzed by inspecting the frequency of choices from each risk level across patients and controls. For this purpose, a repeated measures analysis of variance (ANOVA) was conducted with within-subject factor risk-level (1-number, 2-number, 3-number and 4-number choices) and between-subject factor group (controls, patients). It should be noted that the ANOVA is undetermined for main effects of risk level, since choices from each risk level are mutually exclusive. Thus, the main purpose of this analysis was to show potential interaction effects between group and frequencies of choices from each of the four risk levels. The ANOVA showed a trend interaction between risk-level and group ($F[3, 114] = 2.33$, $p = 0.079$). This trend interaction is illustrated in Figure 3.4.

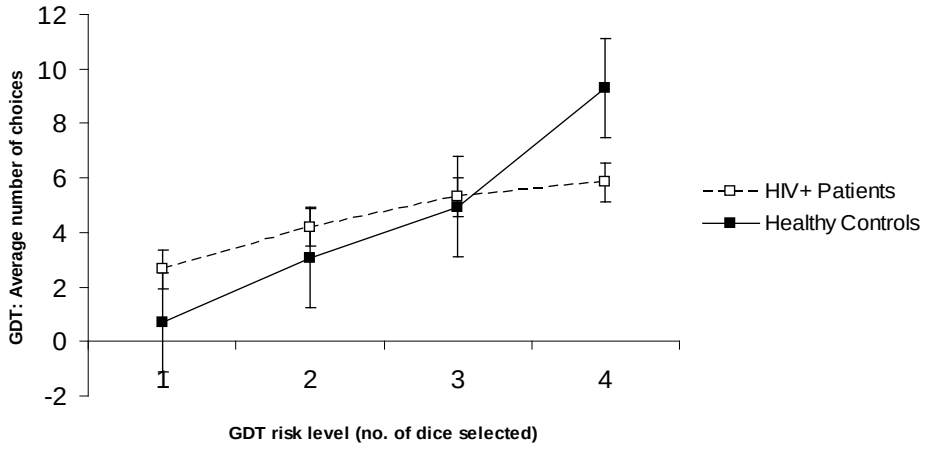

Figure 3.4. Number of choices per risk level in the GDT across groups. Error bars are standard errors of the mean.

As can be seen in Figure 3.4, differences between the two groups were most pronounced for the frequency of the safest choice (4-number choices), although due to the non-significant interaction in the ANOVA, differences were not further followed up.

Further analyses were conducted to determine if patients and controls differed in their response patterns over the course of the task, which could indicate problems with the acquisition of a safe decision strategy. For this purpose, the 18 trials of the GDT were split into three portions: GDT block 1 was made up of trials 1-6, GDT block 2 contained trials 7-12, and GDT block 3 contained trials 13-18. It was then tested a) whether patients differed from controls in their number of safe choices in each block and b) whether the number of safe choices differed across blocks within each group. Patients had fewer safe choices than controls in GDT block 1 ($t[38]= -2.14$, $p= 0.039$) and GDT block 3 ($t[38]= -2.26$, $p= 0.03$). That is, patients started out with riskier choices and while approaching controls' levels in GDT block 2 ($t[38]= -0.94$, $p= 0.352$), they did not continue to improve in GDT block 3. Furthermore, while the number of safe choices never significantly varied across blocks in patients, controls made significantly more safe choices in GDT block 3 than in GDT block 2 ($t[19]= 2.46$, $p = 0.024$). These results are illustrated in Figure 3.5.

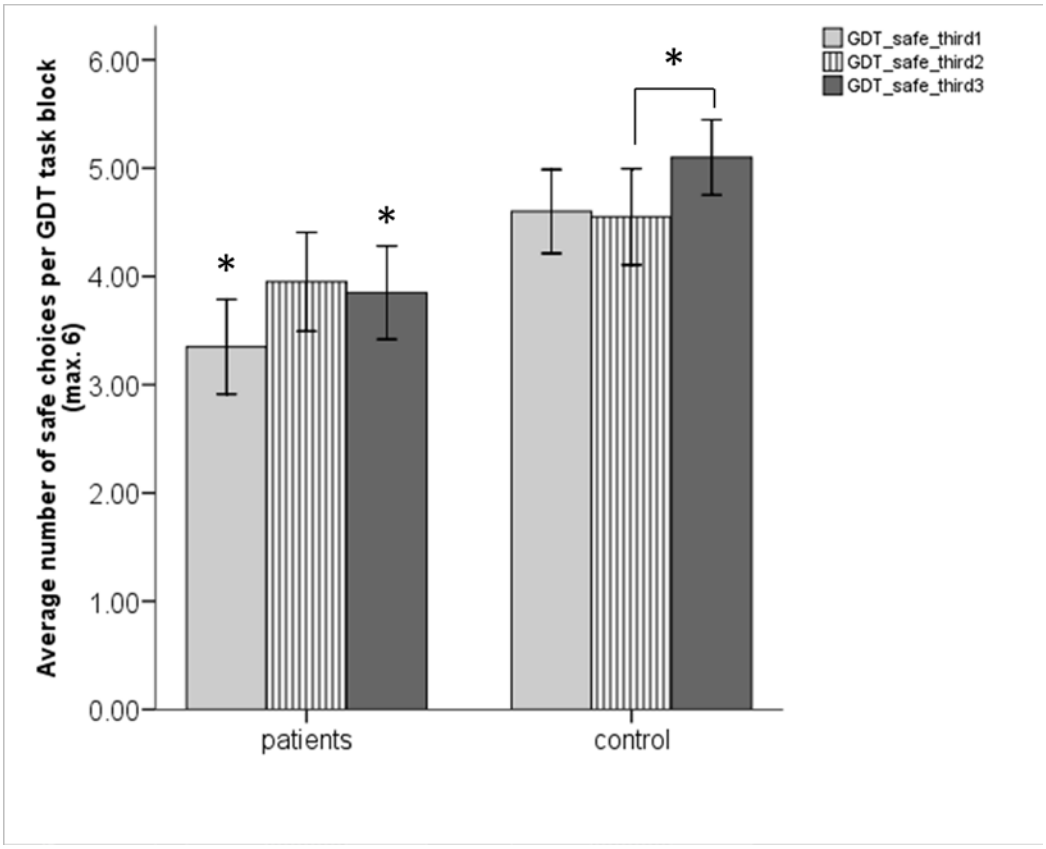

Figure 3.5. Number of safe choices in patients and controls over three GDT task blocks (initial six, middle six and final six GDT trials). *: $p < 0.05$. Error bars are standard errors of the mean.

3.6. GDT Shifts between Risky and Safe Choices

The GDT measure *number of shifts* represents the frequency with which an individual changes their choice strategy by alternating between safe and risky decisions and reflects randomness in the application of a choice strategy (Delazer, et al., 2007). The HIV+ group displayed a trend towards a greater number of shifts between safe and risky decision types than the healthy controls (patients: M= 5.3, SD= 4.22; controls: M= 3.1, SD= 3.28; t[35.8]= 1.84, p= 0.074).

To further follow up on this trend, post-hoc analyses were conducted: first, it was tested whether the number of shifts differed as a function of positive or

negative feedback. Selective differences between patients and controls in this analysis could indicate particular issues with changing one's choice strategy after reward or punishment. Secondly, owing to the finding that patients seemed to be impaired in the development of a safe strategy across GDT task blocks (see above, Figure 3.5), group differences in the number of shifts across task blocks were tested. Thus, it was tested whether patients showed more shifting between safe and risky choices than controls earlier or later during the task.

For this purpose, trial-by-trial contingencies were first inspected regarding shifts from safe (3-number choices and 4-number choices) to risky (1-number choices and 2-number choices) choices and from risky to safe choices as a function of feedback received in the just preceding trial. That is, starting with trial 2, each subsequent trial's choice was coded as a shift after negative feedback or positive feedback, or a non-shift after negative/positive feedback. Table 3.4. outlines all possible response contingencies.

Table 3.4. GDT response contingencies as a function of received feedback.

Case	Previous trial	Feedback	Current trial	Shift/No shift
1	Risky	Negative	Safe	Shift
2	Safe	Negative	Risky	Shift
3	Risky	Positive	Safe	Shift
4	Safe	Positive	Risky	Shift
5	Risky	Negative	Risky	No shift
6	Safe	Negative	Safe	No shift
7	Risky	Positive	Risky	No shift
9	Safe	Positive	Safe	No shift

Only non-shaded contingencies were analyzed.

Owing to the trend increase of shifts in patients compared to controls, groups were compared in the number of shifts after negative feedback (sum of cases 1 and 2, Tab. 3.2) and in the number of shifts after positive feedback (sum of cases 3 and 4, Tab. 3.2). Since the number of trials in which positive or negative feedback was received dictates the number of possible shifts after such feedback, the frequencies of shift numbers was divided by the respective total number of trials in which negative (cases 1 and 2) or positive (cases 3 and 4) feedback was obtained.

As outlined in Table 3.5, patients shifted their current choice strategy in 33.73% of all trials after having received negative feedback in the preceding trial, while controls made such shifts in only 19.19% of trials, a difference that was significant. Patients were significantly more prone to shifting their choices from risky to safe or vice versa compared to controls after having received negative but not after having received positive feedback[ii].

Table 3.5. Percentage of shifts after negative or positive feedback.

	Patients	**Controls**	**Test statistic (df)**	**Significance**
Shifts after negative feedback (cases 1&2)	33.73% (24.90)	19.19% (19.49)	t[38] = 2.057	p = 0.047*
Shifts after positive feedback (cases 3&4)	26.1% (25.85)	16.2% (21.27)	t[38] = 1.322	p = 0.194

Scores are means (standard deviations)

The second follow-up analysis entailed a breakdown of shifts across GDT task blocks. For this purpose, percentages of shifts per block were calculated by dividing the number of shifts in GDT block 1 by five (i.e., GDT block 1 has six trials, but potential shifts can only be made starting with trial 2), and by dividing

the number of shifts in GDT blocks 2 and 3 by six. Patients made significantly more shifts than controls in GDT block 3, mirroring their pattern of reduced safe choices in the final GDT trials (see Table 3.6 and compare Figs. 3.5 and 3.6).

Table 3.6. Percentage of shifting between risk levels withinin each GDT task block (block 1: trials 2-6; block 2: trials 7-12; block 3: trials 13-18).

	Patients	**Controls**	**Test statistic (df)**	**Significance**
GDT task block 1	28% (22.85)	26% (29.81)	t[38] = 0.238	p = 0.813
GDT task block 2	30% (31.71)	16.67% (22.94)	t[34.05] = 1.492	p = 0.145
GDT task block 3	35 % (29.57)	13.33% (21.36)	t[34.58] = 2.657	p = 0.012*

Scores are means (standard deviations)

As can be seen in Figure 3.6, both groups started with an almost identical percentage of shifts between risky and safe choices in the first task block, but while controls successively decreased shifting behaviour, patients increased.

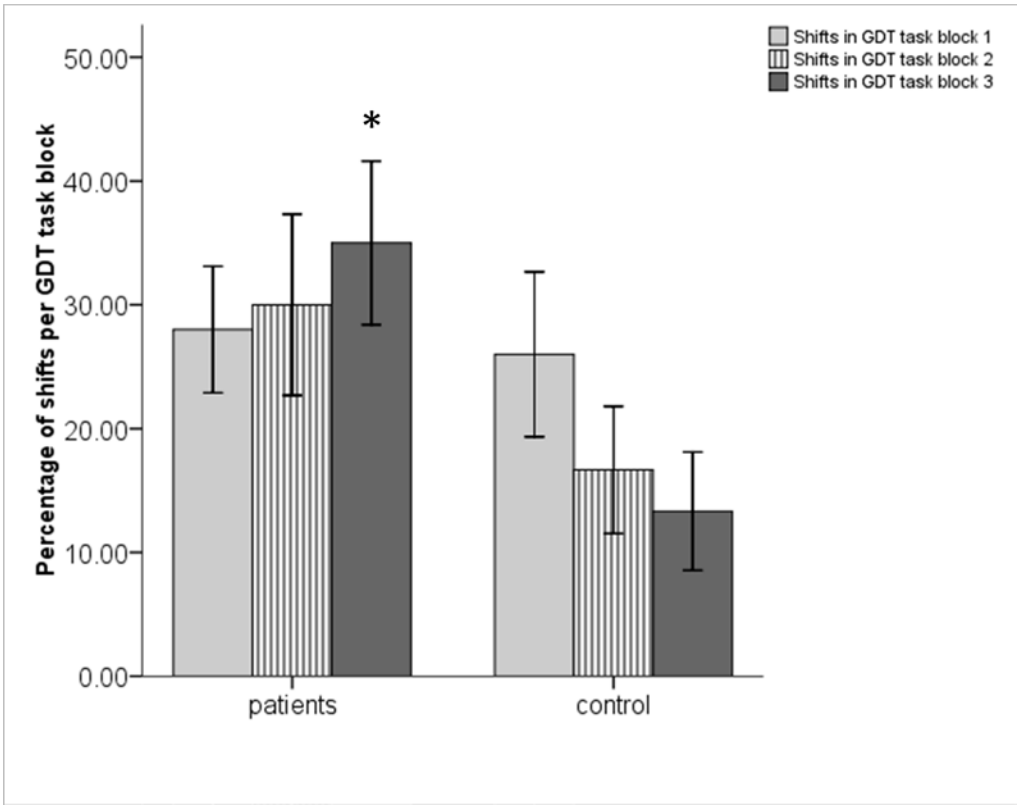

Figure 3.6. Percentage of shifts in each GDT task block (block 1: trials 2-6; block 2: trials 7-12; block 3: trials 13-18). *: $p < 0.05$. Error bars are standard errors of the mean.

3.7. Relationships with Demographic/ Biological Data

First examined were GDT net-score correlations with demographic variables sex (1=male; 2 = female), age, years of education and intelligence within both the control and the HIV+ groups. These were all non-significant, although a negative trend correlation was seen with age ($r[19] = -.43$, $p = .062$) in patients. To test hypothesis three, it was then examined whether GDT was correlated to any of the HIV-specific biological parameters. As can be seen in Table 3.7, GDT net-score was not significantly correlated to the HIV-specific parameters, except for a negative trend correlation with HIV duration ($r[19] = -$

.38, p = .099). Due to the marginal difference between patients and controls in the total number of shifts in the GDT (see above, 3.6), the shift score was also correlated with the biological parameters. A significant relationship between current CD4+ T-cell and the total number of shifts made in the GDT emerged (r[19] = -.49, p = .028). This correlation is illustrated in Figure 3.7.

Table 3.7. Relationships between the GDT (net-score and total number of shifts) and demographic/biological parameters in healthy controls and in HIV+ patients.

	Patients		**Healthy controls**	
	Net-score	Number of shifts	Net-score	Number of shifts
Age (in years)	-.43†	-.28	.02	.10
Sex (1=male; 2 = female)	.16	-.01	.13	.16
Pre-morbid IQ	-.15	-.16	.19	-.09
Years of Education	.01	-.02	-.11	.13
Duration of HIV infection	-38†	-.37	-	-
CD4 nadir	.23	-.29	-	-
CD4 current	.02	-.49*	-	-
Viral load current[1]	.28	.03	-	-

*: $p < .05$; †: $p < .10$; [1]: Spearman rho

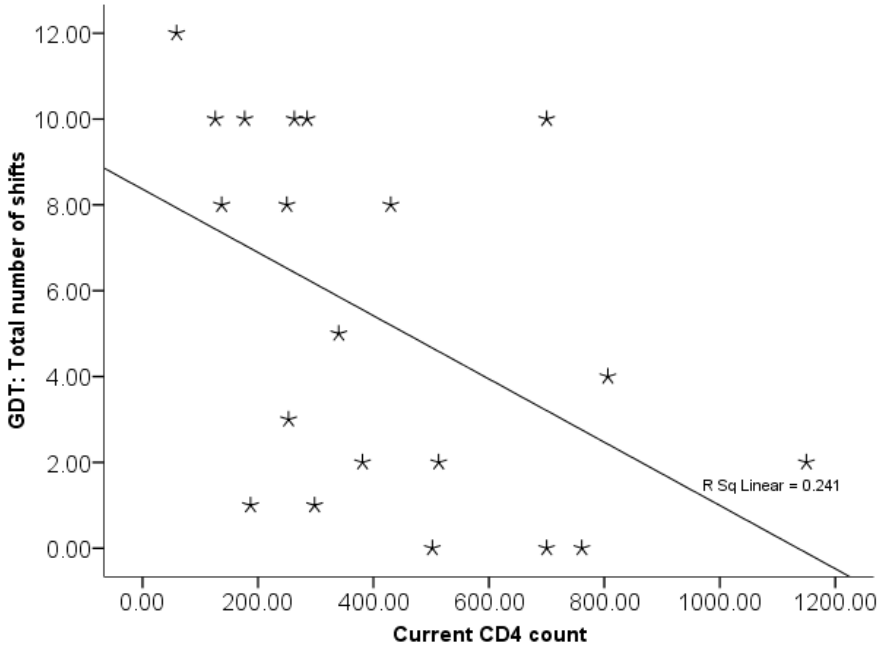

Figure 3.7. Correlation between current CD4+ T cell count and the total number of shifts made during the GDT.

Owing to the negative trend correlation between GDT net-score and age, and that patients' age and duration of HIV infection are confounded, partial correlations were conducted, controlling for age, only in patients and using the same variables as shown above. There were no substantial changes in the correlations when controlling for age (see Table 3.8, compare with Table 3.7). It should be noted that the relationship between current CD4+ T-cell and the total number of shifts in the GDT was slightly higher when controlling for age ($r_{part}[17] = -.54$, $p = .017$). Furthermore, there now was a trend correlation between nadir CD4+ T cell count and the number of shifts in the GDT ($r_{part}[15] = -.42$, $p = .098$).

Table 3.8. Partial correlations between the GDT (net-score and total number of shifts) and demographic/biological parameters in healthy controls and in HIV+ patients, controlling for age

Control variable: Age (in years)	**Patients**	
	Net-score	Number of shifts
Sex (1: male; 2: female)	.19	-.01
Pre-morbid IQ	.15	.02
Years of Education	.13	.05
Duration of HIV infection	-.26	-.30
CD4 nadir	.12	-.42†
CD4 current	-.02	-.54*
Viral load current[1]	.22	-.06

*: $p < .05$; †: $p < .10$; [1]: Spearman rho

In patients only, further partial correlations were conducted between demographic/biological parameters and the additional GDT variables that differentiated between groups during our exploratory post-hoc analyses (GDT sum, GDT number of safe choices in task blocks 1 and 3, GDT shifts after negative feedback, GDT number of shifts in task block 3), but none were significant.

3.8. Relationships with Neuropsychological Performance

Performance on the GDT was then correlated to other neuropsychological measures in the HIV+ and control groups to further test hypothesis three, i.e., that GDT performance should be correlated with cognitive, especially executive functions. Table 3.9 shows all correlations (uncorrected and Bonferroni-corrected).

Table 3.9. Correlations between the GDT (net-score and total number of shifts) and neuropsychological test results in healthy controls and in HIV+ patients.

	HIV+ Patients		Healthy controls	
Domain Test score	Net-score	Number of shifts	Net-score	Number of shifts
Attention/Information Processing Speed				
SDMT	-.05	-.34	.12	-.06
PASAT	-.01	-.18	.06	-.13
D-KEFS TMT-2 time[1]	-.58*	.54*	-.25	.20
D-KEFS Colour Naming time	-.13	.50†	-.15	.18
D-KEFS Word Reading time[1]	-.17	.46†	-.26	.19
Digit span forward	.24	-.19	.41	-.70*
Memory				
SRT immediate recall	.51†	-.36	.21	-.24
SRT delayed recall	.52†	-.14	.37	-.30
ROCF immediate recall	.26	-.30	.12	-.26
ROCF delayed recall	.26	-.23	.15	-.22
Executive Functions/Working Memory				
WCST correct sorts	.69*	.16	.15	-.14
WCST perseverative errors	-.11	.19	-.37	.30
WCST non-perseverative errors[1]	-.53†	-.10	-.25	.18
COWAT perseverations	-.06	.17	.02	.36
SRT intrusions[1]	-.48†	.07	.23	-.10
D-KEFS Inhibition time	-.26	.44	.001	-.04
D-KEFS Color Naming errors[1]	-.36	.39	.29	-.29
D-KEFS Word Reading errors[1]	N/A	N/A	.13	-.11
D-KEFS Inhibition errors[1]	-.72*	.35	.19	-.12
D-KEFS TMT 2 errors[1]	N/A	N/A	-.35	.39
D-KEFS TMT 4 time	-.06	.12	-.04	.13
D-KEFS TMT 4 errors[1]	-.01	.17	-.36	.23
Digit span backwards	.28	-.42	.31	-.46†
Visuo-spatial ability				
ROCF copy[1]	.20	-.34	.08	-.14
Language				
COWAT	.05	.001	.29	-.23
Motor Speed				
Pegboard dominant hand	-.11	.58*	.25	-.34
Pegboard non-dominant hand	-.10	.43	.17	-.28

*: $p < .05$ after Bonferroni-correction for the number of correlations/variables tested within each test instrument; †: $p < .05$, uncorrected; [1]: Spearman rho; N/A: No errors were made

In patients, the GDT net-score was significantly correlated with only one measure of processing speed (TMT-2 time). The hypothesized correlation with executive functions was observed. GDT net-score correlated with correct sorting in the WCST and negatively with errors in the Colour-Word Interference Test of the D-KEFS. Notably, the number of shifts showed neither significant nor trend correlations with executive functions, but solely with psychomotor speed measures (note also the trend correlations within the attention/processing speed domain). In controls, the GDT net-score was uncorrelated with any of the neuropsychological tests. The only test related to the GDT number of shifts in controls was seen with digit span forward, a measure of attention/ short-tem memory.

To control for potential influences of demographic variables age, sex and education on our correlations between GDT and cognitive status, relationships demographics and neuropsychological test scores were examined. In controls, age was correlated with verbal fluency in the COWAT ($r[19]=.60$, $p<.05$, Bonferroni-corrected) and with TMT-4 (Trails B) time ($r[19]=.53$, $p<.05$, Bonferroni-corrected). In patients, the only significant correlation was between age and the WCST – correct sorts ($r[19]= -.56$, $p < .05$, Bonferroni-corrected). To control for potential confounds by age, partial correlations controlling for age were conducted, between the two GDT measures (net-score, number of shifts) and COWAT, TMT-4 time (in controls) as well as WCST – correct sorts (in patients). As prior (cf. Table 3.9), COWAT was unrelated to either GDT measure in controls when age was controlled (net-score: $r_{part}[17] = .29$, $p > .1$; shifts: $r_{part}[17]$

= -.22, p > .1), and so was TMT-4 time (net-score: $r_{part}[17] = -.06$, p > .1; shifts: $r_{part}[17] = .08$, p > .1). Most importantly, the prior correlation between WCST – correct sorts and the GDT net-score (r[18]=.69; cf. Table 3.9) was still significant when controlling for age ($r_{part}[17] = .6$, p < .05, Bonferroni-corrected). GDT number of shifts were unrelated to WCST – correct sorts in patients, controlling for age ($r_{part}[17] = .01$, p > .1).

In addition, to put the previously reported correlations between the GDT and disease parameters (cf. Table 3.7) in perspective to other cognitive variables, the latter relationships were also tested. Nadir CD4+ T cells count was negatively correlated to a single test score, errors in D-KEFS Colour Naming (r[16] = -.59, p<.05, Bonferroni-corrected). Current CD4+ T cells count was related only to TMT-4 (trails B) time (r[16] = -.50, p <.05). Surprisingly, disease duration, controlling for age, was inversely correlated to three measures of psychomotor speed, D-KEFS Colour Naming time ($r_{part}[15] = -.57$, p < .05), Pegboard Dominant Hand time ($r_{part}[17] = -.55$, p < .05), and Pegboard Non-Dominant Hand time ($r_{part}[17] = -.53$, p < .05).

3.9. Questionnaires

None of the questionnaires HADS, DOSPERT and MOS correlated with GDT net-score or GDT number of shifts. Furthermore, demographic and disease-related parameters were not correlated to the questionnaires either. However, a couple of cognitive performance scores showed relationships to the questionnaire data. As can be seen in Table 3.10, severity of depressive symptoms in the HADS, and less so, anxiety symptoms, as well as the overall mental health status

according to the MOS-HIV showed most pronounced relationships to cognition, especially to psychomotor speed. Executive functions that also showed correlations with the questionnaires were either working memory or speed variables such as inhibition time, but not set-shifting in the WCST. The only correlation with the DOSPERT implied that individuals with fewer perseverative errors in the WCST were engaging more in risky actions. This correlation may be a spurious finding; as a similar measure, intrusion errors in the SRT was marginally *positively* correlated with the same DOSPERT subscale, implying the opposite type of relationship.

Table 3.10. Correlations between questionnaires and neuropsychological tests in HIV+ patients only.

Domain Test score	**HADS Anx.**	**HADS Dep.**	**MOS Phys.**	**MOS Ment.**	**DOS A**	**DOS B**
Attention/Information Processing Speed						
SDMT	-.48	-.59*	.33	.43	.25	-.18
PASAT	-.60*	-.52*	.36	.48*	.15	.003
D-KEFS TMT-2 time[1]	.48	.71*	-.25	-.46	-.13	.20
D-KEFS Colour Naming time	.50†	.68*	-.54†	-.55*	-.19	.25
D-KEFS Word Reading time[1]	.50†	.68*	-.21	-.50†	-.31	.14
Digit span forward	-.37	-.49†	.21	.43	-.21	.47
Memory						
SRT immediate recall	-.27	-.29	.08	.20	-.27	.36
SRT delayed recall	-.21	-.36	.30	.27	-.20	.19
ROCF immediate recall	-.14	-.20	.10	.15	-.03	.15
ROCF delayed recall	-.12	-.17	-.02	.08	-.07	.24
Executive Functions/Working Memory						
WCST correct sorts	.06	-.14	.08	.12	.46	-.04
WCST perseverative errors	.10	.27	-.33	-.25	-.60*	.19
WCST non-perseverative errors[1]	-.17	.04	.21	.08	-.10	-.16
COWAT perseverations	.02	.01	.31	.05	-.08	-.06
SRT intrusions[1]	.47†	.41	-.19	-.41	.51†	-.34
D-KEFS Inhibition time	.61*	.79*	-.53†	-.64*	-.04	-.01
D-KEFS Color Naming errors[1]	.05	.11	.26	.02	.05	-.24
D-KEFS Inhibition errors[1]	.31	.27	-.22	-.27	.21	-.30

D-KEFS TMT-4 time	.42	.10	-.07	-.18	.11	-.19
D-KEFS TMT-4 errors[1]	-.08	-.26	.28	.25	.24	-.11
Digit span backwards	-.40	-.53*	.25	.41	-.06	.24
Visuo-spatial ability						
ROCF copy[1]	-.02	-.03	-.02	.11	.01	.11
Language						
COWAT	-.17	-.004	-.22	-.14	.31	-.11
Motor Speed						
Pegboard dominant hand	.43	.70*	-.55*	-.57*	-.08	.28
Pegboard non-dom. hand	.41	.65*	-.49†	-.50†	-.35	.34

*: $p < .05$ after Bonferroni-correction for the number of correlations/variables tested within each test instrument; †: $p < .05$, uncorrected; [1]: Spearman rho; Anx.: Anxiety, Dep.: Depression; Phys.: Physical Health Summary Score; Mental Health Summary Score; DOS A: DOSPERT – A: likelihood to engage in risky actions; DOS B: DOSPERT B – Perceived riskiness of actions

4. DISCUSSION

This study examined differences in decision making under risk in an HIV+ population in comparison to healthy controls as well as relationships between decision making, neuropsychological functioning and biological factors. The HIV+ population displayed impairments in decision making under risk, extending previous findings in HIV+ and decision making under ambiguity. Decision making under risk was related to HIV patients' cognitive, especially to processing speed and executive functions and to current immune functioning.

4.1. Pattern of Neuropsychological Impairment in the HIV+

The HIV+ population displayed impairment across multiple cognitive domains compared to the healthy controls, specifically attention and information processing speed, executive functions including verbal fluency, and psychomotor speed. This pattern of impairment confirms the hypothesis that the HIV+ group would display deficits in neuropsychological testing compared to the healthy control group in multiple domains and especially so, motor skills, speed of information processing, attention and executive functioning. The patients displayed a similar pattern of impairment compared to previous studies of HIV+ groups, specifically individuals in a post-cART era (Cohen, 2009; Grant, 2008). The HIV+ group also performed normally in some domains, including visuospatial construction of the Rey Osterrieth Complex Figure and its recall, similar to previous HIV studies with this task (Albert, et al., 1995; Di Sclafani, et al., 1997; Pereda, et al., 2000). While learning in the Verbal Selective Reminding Task was impaired at immediate test, retention/delayed memory were unimpaired.

Although verbal learning in HIV patients is more commonly examined with different word list learning tests (e.g., the California Verbal Learning Test, or the Hopkins Verbal Learning Test), more pronounced difficulties with acquisition rather than retention of verbal materials have been noted across several previous studies (Becker, et al., 1995; Grant, 2008; Heaton, et al., 1995; Murji, et al., 2003). Thus, taken together, our results are comparable with previous neuropsychological findings in HIV and confirm that our patient sample had a rather typical cognitive impairment pattern.

4.2. Decision Making Impairment in HIV+

The second hypothesis was that the HIV+ group would have poorer performance on a test of decision making under risk (i.e., the GDT) compared to the healthy control group; this hypothesis was confirmed. The HIV+ group in this study displayed impaired decision making under risk; this was reported to be true regardless of intelligence. Multiple indices of task performance implied impairment in the patients, including a lowered net-score (safe – risky choices) and less money won in the task. Indicating disturbances in developing and maintaining a consistent decision strategy, patients also showed more shifts between risky and safe decisions in the GDT than controls. Patients' shifting became successively more frequent as the task progressed, while this behaviour decreased in controls.

Comparing the current findings to the existing small number of decision making studies in HIV, there is general agreement, even though direct comparisons are difficult to draw based on the heterogeneity of the samples, ways

in which decision making was measured and analysed, and the range of neuropsychological tests included in previous studies. HIV patients were impaired in all IGT decision making studies (Gonzalez, et al., 2010; Hardy, et al., 2006; Iudicello, et al., 2013; Martin, et al., 2013; Martin, et al., 2004; Thames, et al., 2012), as they were here in the GDT. One single study assessed decision making under risk (Martin, et al., 2013), but reported no impairment in HIV+ patients.

From this limited literature it would appear that there exists some type of decision making impairment that may be directly related to HIV+. The involvement of fronto-striatal brain areas in HIV as well as the importance of these areas for many aspects of decision making is suggestive in this regard (even though the direct structural or functional brain correlates of such deficits in HIV patients have not been studied yet).

A number of factors in previous decision making studies' HIV populations complicate this interpretation. First, all previous HIV samples in these studies included a substantial percentage of patients with past or present substance abuse. For example, 43% of the 67 HIV patients in Hardy and colleagues (2006) had past and 5% had present drug abuse. In Iudicello and colleagues (2012), 62% of 78 HIV+ patients without cognitive impairment (HAND-) and 73.5% of 68 HIV+ patients with HAND+ had past [>1 month] drug abuse. In Thames and colleagues', (2012) a sample of 100 HIV+ patients, 61% were classified as having past 'substance use' (not further detailed). Three studies exclusively sampled drug using HIV-patients (Gonzalez, et al., 2010; Martin, et al., 2013; Martin, et al., 2004).

Although these samples may be ecologically valid representations of the present North American HIV demographic (all six studies were conducted in the U.S.), substance use disorders *per se* are among the best documented conditions to affect decision making in the IGT (Barry & Petry, 2008; Hanson, Luciana, & Sullwold, 2008; Kjome, et al., 2010; Verdejo-Garcia, et al., 2007). Therefore, unique contributions of HIV serostatus to decision making performance are difficult to discern, at least in studies including patients with and without past/current drug use.

To address this issue, the three studies with mixed HIV+ samples (patients with and without past drug use) statistically controlled whether there was a separate influence of a positive drug history on decision making (Hardy, et al., 2006; Iudicello, et al., 2013; Thames, et al., 2012). Although none of the reported that a positive drug history independently influenced IGT performance, the samples were not optimized to assess such either. That is, the nuisance variable 'presence of (past) drug abuse' (or 'substance use' in Thames et al., 2012) comprised non-descript numbers and types of substances, and did not stratify severity and length of (ab)use or length of abstinence, important factors when assessing relationships between drug abuse and decision making (Hanson, et al., 2008).A composite nuisance measure to approximate an index of a positive drug history is unlikely to reveal substantial influences on cognition, including decision making.

The three studies with drug-using HIV+ and HIV- samples (Gonzalez et al. 2005; Martin et al., 2004; 2013) provide more detailed drug histories. Decision

making performance in the IGT was used as a predictor (not as a dependent variable) for self-reported risky sexual behaviours in Gonzalez and colleagues (2005). The only result reported that included the IGT showed a marginally significant regression model in which sensation seeking in conjunction with *good* IGT performance predicted risky sexual behaviours more in the HIV+ than in the HIV- group. Executive functions (response inhibition [Stroop], working memory) were also assessed but did not contribute to the prediction of risky sexual behaviours over and above sensation seeking. Direct group differences in IGT were not reported and neither were relationships between IGT and executive functions, rendering Gonzalez and other's (2005) results difficult to evaluate in the current context.

Martin and colleagues (2004; 2013) reported IGT deficits in their HIV+ samples compared to drug-using HIV- controls. HIV+ patients and controls were demographically well matched in two studies. However, HCV infection rates were not provided. This was the case even though about 60% in each of the samples were injection drug users in Martin et al. (2004). Rates of injection drug use are not reported in Martin et al. (2013), but between 2% and 14% of either HIV+ or HIV- participants reported past or current opioid use. In addition, HIV+ individuals in the latter study also reported slightly more opioid addiction severity. Even though this rate was not significantly different from that of the control group ($F=1.98$, $p=.16$), controlling for opioid addiction severity rendered the IGT difference between the groups a trend effect. Thus, injection drug use and

potential HCV (co-)infection could have played a role in Martin and colleagues' results.

In addition, across all studies, many patients were only partially immune-suppressed (detectable viral loads were observed in 41% of HAND- HIV+ patients in Iudicello et al, [2012], in substance-dependent HIV patients in Martin et al, [2013; 69% of similar patients in Martin et al. 2004], and up to 67% of patients in Thames et al. [2012]). Significant differences in demographic variables existed between patients and controls in some of the studies (Hardy, et al., 2006; Thames, et al., 2012).

In contrast, our study included a small but highly selected HIV+ group. Patients were all free of current drug abuse and had no significant, recent substance abuse (within the last five years). None of them had HCV co-infection or had ever used injection drugs. The HIV group was further matched to the healthy control group on the basis of sex, age, education and intelligence. Detectable viral load was only present in 3/20 (i.e., 17% of the patients). Thus, using a less complicated population, the results of the current study can more reliably be attributed to disease-related factors. Of note here as well is that even though at least some biological parameters of disease activity were assessed in all previous HIV decision making studies, these were never examined in direct relationship to decision making performance. This is discussed in more detail in section 4.3.

When comparing the previous IGT-HIV+ studies with the current study using the GDT, it is critical to interpret results in light of the different types of

decision making each task is measuring. As noted in section 1.2.1, the IGT overall, is believed to assess ambiguous decision making but when splitting the analysis across task blocks or trials, later trials (usually task blocks 3-5, trials 41-100) are thought to represent decision making under risk, whereas earlier trials are assumed to more purely assess decision making under ambiguity (e.g., Brand, et al., 2007b). Some of the studies, but not all (Martin, et al., 2013; Martin, et al., 2004) reported IGT impairment in HIV+ samples particularly or exclusively in later trials of the IGT (Hardy, et al., 2006; Iudicello, et al., 2013: Thames, et al., 2012). Latter studies may suggest a possible influence of executive or other cognitive functions on IGT performance in HIV patients, rather than that of emotional or implicit functions. The current study's correlation patterns with decision making are discussed in the next section.

4.3. Relationships with Cognitive and Biological Variables

The third hypothesis predicted that cognitive functions, especially executive functions, and biological parameters of disease severity would co-vary with decision making in the GDT in HIV patients. Evidence in favour of this prediction was reported. Overall quality of decision making (GDT net-score) correlated with performance in executive function tests (correct sorts in the Wisconsin Card Sorting Test, errors in the D-KEFS Inhibition trial of the Colour-Word Interference Test) and in processing speed/attention (D-KEFS Trail Making Test-2). GDT shifting behaviour correlated with processing speed/attention (D-

KEFS Trail Making Test-2), psychomotor speed (Pegboard), current CD4+ T-cell count, and showed a trend correlation to nadir CD4+ T-cell count.

The one study assessing decision making under risk in HIV (using the Cups Task; Martin, et al., 2013) reported no impairment in patients. The Cups Task differs from the GDT in important ways: even though the probabilities and decision outcomes are explicitly displayed in both tasks, they change in each trial of the Cups Task. That is, participants make decisions on a trial-by-trial basis and do not have to develop a long-term strategy for solving the task. Instead, they are visually prompted in each trial of the Cups Task about what an optimal decision strategy might be in the current trial. The (unimpaired) Cups Task performance in Martin et al.'s (2013) HIV-patients also did not correlate with any of the assessed measures of executive functions. The only reported correlation was between Cups Task 'risk aversion' and a measure of verbal long term memory, implying that patients with lower memory were more risk averse. The GDT contains no memory component and explicitly displays the same contingencies throughout all 18 trials; thus, correlations with episodic memory are not expected. To this end, Labudda et al. (2009) examined medial temporal lobe epilepsy patients (i.e., patients with a compromised hippocampus and/or amygdala). The patient group was able to perform the GDT, but failed to successfully navigate the IGT. IGT deficits were reported even in patients with only hippocampal damage, independent of amygdala damage (Labudda, et al., 2009). This pattern of findings implies an important role of limbic/medial temporal lobe regions associated with emotional and episodic memory functions in IGT performance, but not in GDT

performance. Thus, relationships between GDT performance and memory were neither expected nor reported here.

As mentioned above, some IGT decision making studies in HIV+ samples reported IGT deficits specifically in later task trials (Hardy, et al., 2006; Iudicello, et al., 2013; Thames, et al., 2012). As this part of the IGT is considered to reflect some degree of explicit knowledge about the decision contingencies (Brand, et al., 2007b), less reliance on emotional feedback processing, and more reliance on strategic planning and strategy maintenance (i.e., executive functions), one would expect correlations between decision making deficits and executive dysfunctions in these studies, as was the case in all three studies. Executive function composite scores (Thames, et al. [2012]: Trail Making Test B, Short Category Test, Stroop Test; Iudicello, et al. [2013]: Wisconsin Card Sorting Test – number of perseverative errors; Trail Making Test B minus A) were correlated with patients' IGT performance in task blocks 3-5. In Hardy and colleagues (2006), selections of deck B (often noted as the most risky, 'going for broke' choice in the IGT) were increased in patients only in blocks 3-5, but correlations between deck B choices and cognition were calculated across the entire IGT, showing relationships with Stroop Test performance. Even though Martin and colleagues (2013) did not observe group by IGT task block interactions and reported HIV+ patients impaired across the entire task (and especially so, in *earlier* task blocks), they calculated correlations between cognitive test results and performance in IGT task blocks 4-5 and reported a correlation with Stroop test performance. Martin and colleagues (2004) reported that HIV+ patients scored lower than controls in the

entire IGT, but failed to find a relationship with working memory performance in a delayed-match to sample task. Finally, Gonzalez and colleagues (2010) examined specifically the *earlier* parts of the IGT and whether implicit learning (procedural memory tests) would covary with HIV+ patients' IGT performance. They failed to find any relationships between procedural memory and IGT performance, however.

Thus, most of the existing studies could confirm relationships between IGT performance, especially in later trials, and executive functions. However, the relationships were not always exclusively with executive functions. As such, relationships were also reported with verbal learning (Hardy, et al., 2006) or depression (Thames, et al., 2012). The HIV+ findings of the current study concur generally with this literature, finding correlations between decision making under risk in the GDT (i.e., most equivalent to late IGT trials) and executive functions. However, the current study also reported other cognitive functions, attention and psychomotor speed, correlated with GDT performance. Interestingly, shifting behaviour in the GDT was more consistently related to attention/speed measures in the current study than to executive functions. This finding is similar to Delazer et al.'s (2007) study with early stage Alzheimer Disease patients. Although these patients were not impaired in the GDT overall, they showed increased shifting behaviour in the GDT similar to the HIV+ patients here, and especially so towards the end of the task. Shifting behaviour in Delazer et al. (2007) was also significantly correlated with performance in the Trail Making Test A (attention), as well as with Trail Making Test B (executive function: cognitive flexibility), but

not with a number of other tested executive functions. In addition, considering conceptual ambiguities with the division of IGT task blocks to determine whether the IGT measures decision making under ambiguity (early task blocks) or decision making under risk (later task blocks), the current study with the GDT, i.e., a task that eliminates elements of decision ambiguity altogether, renders a more definitive measure of decision making under risk.

Secondly, one should consider conceptual issues with the IGT regarding the interpretation of performance by task block. As the IGT assesses decision making under ambiguity that, if considering block-wise performance, is supposed to switch at some point during the task into decision making under risk (i.e., when participants understand the rules), the demarcation of 'blocks' within the IGT is somewhat arbitrary. That is, analysing the IGT by blocks of task performance, although approximating measures of decision making under ambiguity versus risk, will necessarily be imprecise because different participants will acquire explicit knowledge about the risks associated with each choice at different points in time throughout the IGT. As a result, the precise role of executive functions in HIV+ patients' decision making performance is not clear based on the previous IGT studies. A task that eliminated elements of decision ambiguity altogether, the GDT that was used here, renders a more definitive measure of decision making under risk. The current findings imply that GDT net-score and GDT shifting behaviour indicate two somewhat separable deficits in HIV+ patients. As such, the overall quality of decisions across the task was related to executive functions, while attention/psychomotor speed, as well as current CD4+T-cell count (less

pronounced: nadir CD4+ T-cell count) were related to shifting behaviour in the GDT. Although speculative, one could assume that the ability to identify and then maintain beneficial decisions throughout the entire task (GDT net-score) may have been associated with HIV+ patients' frontal lobe changes in this study, whereas subcortical areas may have driven erratic choices from trial to trial (GDT shifting). This interpretation is also supported by patients' selective impairment in utilizing feedback for their choices. Feedback processing and the execution of motor actions in response to positive and negative reinforcement are crucially mediated by striatal/midbrain areas (i.e., subcortical areas) of the brain (Brooks & Berns, 2013; Marco-Pallares, Muller, & Munte, 2007; Palminteri, et al., 2012). The finding of a selective impairment in *negative* feedback processing here resembles previous GDT findings in other samples with assumed structural or functional (fronto-)subcortical pathologies [pathological gambling, Parkinson's and opiate addiction; see (Brand, et al., 2005; Brand, et al., 2004; Brand, Roth-Bauer, Driessen, & Markowitsch, 2008)]. The reason why *positive* feedback utilization did not differentiate the groups here is likely due to only the shifting behaviour was analysed. Positive feedback is considerably more likely incurred after safe choices than after risky choices and in this case should motivate *persistence* on safe choices rather than shifting. Therefore, not finding group differences in shifting behaviour after positive feedback is not surprising.

As patients were more consistently impaired across all assessed (subcortical) attention and speed measures than across (frontal) executive functions, correlations between the GDT scores that were related to

attention/speed and biological parameters of HIV disease severity may also make sense. The relationship between biological indicators related to HIV and neurocognitive functioning has been documented widely although variation in findings exists. Given the current era of HIV treatment, it was expected that if any biological relationships were present these would most likely be between the nadir CD4+ T-cell count and cognition. There was no relationship between the GDT net-score and the nadir CD4+ T-cell measure but a trend relationship with GDT shifts. Failure to detect a strong relationship between nadir CD4+ T-cell count and neurocognitive performance could be due to a lack of power. Considering the small sample size and large variation in this measure, it was particularly unfortunate not to be able to obtain nadir CD4+ T-cell counts in two of the 20 patients. The study did reveal a significant relationship between GDT shifts and the *current* CD4+ T cell count (available for all 20 patients). No other previous investigation of decision making in HIV directly tested relationships with biological disease markers. The current CD4+ T cell count is a marker for current immune function. As such, with better immune functioning and higher current CD4+ T-cell count, there was less shifting in the GDT and individuals in a better state of health were better able to successfully engage in advantageous decision making[iii]. It should be noted, however, that the biological disease markers were generally not indicative of cognition in the current sample. Only two relatively isolated correlations were observed, one between attention and nadir CD4+ T-cell count and one between cognitive flexibility and current CD4+ T-cell count.

Therefore, the GDT-findings in relation to immune function, although suggestive, should not be overstated.

4.4. Additional Findings

In addition to the three primary hypotheses a number of secondary findings warrant discussion. An important finding was that the GDT measures (net-score and shifts) did not have any relationship to measures of anxiety, depression, or measures from the MOS-HIV. Unlike the IGT which is – by definition – also intended to assess emotional functions, and has been reported to covary with comorbid depression in HIV (Thames, et al., 2012) and other neurological conditions (Simioni, et al., 2008), the GDT is less often influenced by decreased mood (e.g., Bayard, Yu, Langenier, Carlander, & Dauvilliers, 2010; Matthies, Philipsen, & Svaldi, 2012; but see Svaldi, Philipsen, & Matthies, 2012). A lack of relationships with the MOS-HIV tool is insightful in that it suggests that despite an apparent impairment of decision making, the impacts are not directly associated with perceived health or functional status. As the MOS-HIV and HADS did reveal a number of substantial relationships with other areas of cognitive functioning, the lack of correlations with the GDT is unlikely an artifact of our small sample size. The current findings in this regard are similar to findings of Iudicello et al. (2012). In their study, IGT performance (in blocks 3-5) was not predictive of deteriorations in HIV-patients' instrumental activities of daily living, employment status or medication adherence. Cognitive status (HAND/no HAND) was related to activities of daily living and employment status, while psychiatric problems were related to medication adherence. Although adequate decision

making would appear to be a critical function in everyday life, it was not substantially related to perceived functional impairment in the HIV patients, at least not when assessed by self-report.

4.5. Limitations

Primary limitations of this study are related to the population of interest. The complicated nature of the HIV+ population limits the ability to control potentially confounding comorbidities. Although a highly selected group was enrolled here, a larger sample would have allowed for more definitive answers regarding the extent of HIV-patients' decision making impairment as well as relationships with other functions or biological parameters. Increased statistical power with larger sample sizes, especially when examining relationships with the nadir CD4 T+ cells counts, would have been desirable.

When designing the procedures for the study various tests of interest had to be excluded in light of time limitations. As all previous decision making studies in HIV have employed the IGT, an investigation using both the IGT and GDT together with the same patient population would be particularly interesting. Such a study would allow differentiation of the two types of decision making within a single HIV+ population (as in Martin et al., 2013).

The current study included numerous tests to assess neurocognitive function, risk taking and health status. With so many tests, and thus variables, type I errors needed to be controlled. Although this was done here by application of Bonferroni-corrections within tests, such corrections could still be too liberal.

Some previous investigations of HIV and decision making have used composite scores derived from published norms to characterise neuropsychological functions in broader cognitive domains and circumvent similar problems with type I errors (Iudicello, et al., 2013; Thames, et al., 2012). Derivation of such composite cognitive domain scores is desirable on statistical grounds, but does prevent finer-grained analyses of relationships between decision making and each test. Furthermore, composite scores require either theoretical consensus or statistical (e.g., factor analysis) methods prescribing the inclusion of specific tests into domains, both of which were not possible with the current study. As such, the control group was too small to allow factor analytical derivation of possible domain scores. The test battery also had a disproportionate representation of executive function tests so that a theoretical derivation of cognitive domain scores likely would have been biased. Finally, using published norms to derive measures of normative performance critically depends on the appropriateness of the norm samples for each test. In this regard, decision making impairments were evident in (norm-based) cognitively *intact* HIV patients in Thames et al. (2012), whereas decision making impairments were confined to (norm-based) cognitively *impaired* HIV patients in Iudicello et al. (2013). These conflicting findings may indeed have been partly due to different normative samples used to quantify cognitive functions in the HIV patients in these two studies.

5. CONCLUSION

Decision making under risk in the GDT was impaired in a sample of HIV patients with few confounding comorbidities. This finding recapitulates previous studies of decision making under ambiguity assessed with the IGT. The present study provides a clearer understanding of risky decision making in showing cognitive aspects of decision making impaired and related to executive dysfunctions in an HIV+ population. The relationship between decision making and current CD4+ T cell count (as well as the trend correlation with nadir CD4+ T cell count) is a novel finding in the decision making literature in HIV and should be examined further in future studies. Despite improvements in treatment and outcome of HIV, cognitive dysfunctions remain a significant concern. Decision making is a complex but ubiquitous activity of daily life, and should be considered a critical implication in HIV.

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APPENDIX

Table A.1. Revised research criteria for HIV-associated neurocognitive disorders.

HIV-associated asymptomatic neurocognitive impairment (ANI)*

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
2. The cognitive impairment does not interfere with everyday functioning.
3. The cognitive impairment does not meet criteria for delirium or dementia.
4. There is no evidence of another preexisting cause for the ANI.†

**If there is a prior diagnosis of ANI, but currently the individual does not meet criteria, the diagnosis of ANI in remission can be made.*

†If the individual with suspected ANI also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of ANI should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

HIV-1-associated mild neurocognitive disorder (MND)*

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills. Typically, this would correspond to an MSK scale stage of 0.5 to 1.0.
2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):
    a) Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
    b) Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.
3. The cognitive impairment does not meet criteria for delirium or dementia.
4. There is no evidence of another preexisting cause for the MND.†

**If there is a prior diagnosis of MND, but currently the individual does not meet criteria, the diagnosis of MND in remission can be made.*

†If the individual with suspected MND also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

HIV-1-associated dementia (HAD)*

1. Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be done as indicated in algorithm; see below). Typically, this would correspond to an MSK scale stage of 2.0 or greater.
2. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities).
3. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.
4. There is no evidence of another, preexisting cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse compatible with CNS disorder).†

**If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of HAD in remission can be made.*

†If the individual with suspected HAD also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of HAD should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following cessation of substance use. Note that the consensus was that even when major depression and HAD occurred together, there is little evidence that pseudodementia exists and the cognitive deficits do not generally improve with treatment of depression.

From Antinori, et al. (2007)

Table A.2. Neuropsychological Tests, Bonferroni-corrected significance levels and Normality Violations in Test Scores

Domain Test score	**Bonferroni-corrected significance level**	**Normality violated**
Attention/Information Processing Speed		
Symbol-Digit	n/a	
PASAT	n/a	
D-KEFS TMT-2 time	$p < 0.025$ (0.05/2: time, errors)	X
D-KEFS Colour Naming time	$p < 0.025$ (0.05/2: time, errors)	
D-KEFS Word Reading time	$p < 0.025$ (0.05/2: time, errors)	X
Digit span forward	$p < 0.025$ (0.05/2: forwards, backwards)	
Memory		
SRT immediate recall	$p < 0.017$(0.05/3: immediate, delayed, intrusions)	
SRT delayed recall	$p < 0.017$(0.05/3: see above)	
ROCF immediate recall	$p < 0.017$(0.05/3: copy, immediate, delayed)	
ROCF delayed recall	$p < 0.017$(0.05/3: see above)	
Executive Functions/Working Memory		
WCST correct sorts	$p < 0.017$ (0.05/3: correct sorts, perseverative errors, non-perseverative errors)	
WCST perseverative errors	$p < 0.017$ (0.05/3: see above)	
WCST non-perseverative errors	$p < 0.017$ (0.05/3: see above)	X
COWAT perseverations	$p < 0.025$(0.05/2: total, perseverations)	
SRT intrusions	$p < 0.017$(0.05/3: see above)	X
D-KEFS Inhibition time	$p < 0.025$ (0.05/2: time, errors)	
D-KEFS Color Naming errors	$p < 0.025$ (0.05/2: see above)	X
D-KEFS Word Reading errors	$p < 0.025$ (0.05/2: see above)	X
D-KEFS Inhibition errors	$p < 0.025$ (0.05/2: see above)	X
D-KEFS TMT 2 errors	$p < 0.025$ (0.05/2: see above)	X
D-KEFS TMT 4 time	$p < 0.025$ (0.05/2: time, errors)	
D-KEFS TMT 4 errors	$p < 0.025$ (0.05/2: see above)	X
Digit span backwards	$p < 0.025$ (0.05/2: see above)	
Visuo-spatial ability		
ROCF copy	$p < 0.017$(0.05/3: see above)	X
***Language*:**		
COWAT	$p < 0.025$(0.05/2: see above)	
***Motor*:**		
Pegboard dominant hand	$p < 0.025$ (0.05/2: dominant, non-dominant)	
Pegboard non-dominant hand	$p < 0.025$ (0.05/2: see above)	

Table A.3 cART medications of HIV+ infected patients at the time of study

	Patient Number																			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
cART drug																				
NRTI																				
Abacavir			X		X								X	X		X			X	
Azidothymidine		X																		
Emtricitabine				X		X	X			X	X	X			X		X		X	
Lamivudine	X		X		X		X						X	X		X				
Tenofovir	X			X		X	X			X	X	X			X		X			X
NNRTI																				
Efavirenz			X								X	X		X			X			
Etravirine									X											X
Nevirapine													X							
PI																				
Atazanavir										X					X					
Darunavir									X											X
Lopinavir	X	X			X											X				
Ritonavir	X	X			X				X	X					X	X			X	X
EI																				
Maraviroc				X		X														
II																				
Raltegravir				X		X														X

EI: entry inhibitor, **II**: integrase inhibitor, **NRTI**: nucleoside/nucleotide reverse transcriptase inhibitor, **NNRTI**: non-nucleoside reverse transcriptase inhibitor, **PI**: protease inhibitor

Table A.4. Comparison of study controls with published norms

	Z-Score Mean (SD)
Symbol-Digit	.55 (1.41)
PASAT	.18 (1.01)
D-KEFS TMT-2 time	.19 (1.12)
D-KEFS TMT 4 time	.42 (.63)
D-KEFS Colour Naming time	.06 (.79)
D-KEFS Word Reading time	.28 (.55)
D-KEFS Inhibition time	.41 (.78)
SRT immediate recall	.07 (1.14)
SRT delayed recall	.34 (1.06)
ROCF immediate recall	.17 (1.01)
ROCF delayed recall	.11 (1.04)
WCST perseverative errors	-.16 (.45)
SRT intrusions	.15 (1.29)
Digit span	.54 (.81)
COWAT	.53 (1.00)
Pegboard dominant hand	-.81 (1.14)
Pegboard non-dominant hand	-.71 (1.18)

ENDNOTES

[i] HAART/ and cART are used interchangeably in theHIV literature. to describe the same treatment regimes. For consistency, the term cART is used herein this document as the more accurate and contemporary terminology.

[ii] The types of shifts (risky-to-safe and safe-to-risky) as a function of prior feedback were also analyzed. Patients did not differ significantly from controls in any single one of the cases 1 to 4 in Table 3.2.

iii Of note, despite current treatment with cART, five out of the 20 HIV patients currently had CD4+ T-cell counts in the AIDS defining range (i.e., counts of 200 or less). This number was too small to permit additional sub-groupings within patients and therefore no further analyses with this potentially interesting variable were conducted.