Antiretroviral Therapy and Neurocognitive Functions in People Living with HIV

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ABSTRACT

Despite the wide-spread availability of modern, combination antiretroviral therapy (cART), neurocognitive impairment persists among some people living with HIV (PWH). Among the multiple, interrelated HIV-associated, comorbid, and demographic factors related to neurocognitive problems in HIV today are also potential negative effects of cART (Nightingale et al., 2014; Saylor et al., 2016). We investigated two main questions: 1) What is the relationship between cumulative cART exposure and neuropsychological impairment in PWH? and 2) Based on evidence from existing HIV cohorts, what is the evidence on relationships between cART and memory functions in PWH?

To address the first question, we evaluated the role of ART exposure as predictor of neurocognitive impairment using univariate analyses and machine learning, while accounting for potential effects of demographic, clinical, and comorbidity-related risk factors in a cohort of 343 PWH. Out of a total of 26 tested variables, two random forest analyses identified the most important characteristics of a neurocognitively impaired group (N=59): Compared to a neurocognitively high performing group (N=132; F1-score=0.79), we uncovered 13 important risk factors; compared to an intermediately performing group (N=152; F1-score=0.75), 16 risk factors emerged. Longer lifetime ART-exposure, especially to integrase inhibitors, was one of the most important predictors of neurocognitive impairment in both analyses (rank 2 of 13 and rank 4 of 16, respectively), superseding effects of age (rank 11/13, rank 15/16) and HIV duration (rank 13/13, rank 16/16). Concerning specific integrase inhibitors, the impaired group had significantly longer dolutegravir exposure (p=.011) compared to the high performing group (p=.012; trend compared to the intermediate group p = 0.063).

To address the second question, we conducted a systematic review of the current literature on memory functions in cART-treated HIV cohorts. An initial search of four major databases (EMBASE, CINAHL, MEDLINE and PsycINFO) resulted in 4,080 records with 82 potentially relevant full texts. After screening, 31 studies were ultimately included in the review. Of the 31 included studies, 10 were longitudinal and 21 were cross-sectional (two clinical trials and 29 observational studies). Among the longitudinal studies, 7/10 showed improved (verbal) memory in PWH after initiation of cART, with evidence from four comparable studies pointing to effects specifically in patients with impaired memory at baseline. Among the cross-sectional studies, we found equal evidence for reduced (n=7 studies) or similar (n=7 studies) memory performance in PWH compared to the respective control groups. These studies showed no difference in the percentage of PWH receiving ART ($\chi^2[36]=22.49$, p=.29). Substantial heterogeneity of the included memory measures, study designs, and cohorts, as well as a lack of specific cART information in the identified cohort studies impeded our ability to draw further conclusions from this literature.

Understanding the relationship between cART and cognition remains a challenge in HIV research and care, one that is imperative to solve considering the aging demographic in cART-treated PWH today. Apart from retrospective work such as presented in this thesis, more longitudinal studies, ideally randomized controlled trials, as well as experimental work on specific drug-cognition relationships are needed. Information from such studies may further help clinicians optimize treatments strategies for PWH, ultimately leading to increased quality of life for patients.

PREFACE

Chapter 3 is a reprint of Amusan et al. (2020), “Lifetime Antiretroviral Exposure and Neurocognitive Impairment in HIV”, Journal of Neurovirology, vol. 26, issue 5, pages 743-753, doi:10.1007/s13365-020-00870-z

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List of Abbreviations

AAN: American Academy of Neurology

AIC: Akaike's Information Criterion

AIDS: acquired immunodeficiency syndrome

ANI: asymptomatic neurocognitive impairment

ART: antiretroviral therapy

AUC: area under the receiver operating curve

AZT: zidovudine

BIC: Bayesian Information Criterion

BVMT: Brief Visuospatial Memory Test-Revised

cART: combination antiretroviral therapy

CD4 cells: CD4 T-lymphocyte cells

CES-D: Centre for Epidemiological Studies Depression Scale

CNS: central nervous system

CPE: CNS-penetrance effectiveness

CVLT: California Verbal Learning Test

Del: delayed

D-KEFS: Delis-Kaplan Executive Function System

GPB: Grooved Pegboard

HAD: HIV-associated dementia

HAND: HIV-associated neurocognitive disorders

HCV: Hepatitis C Virus (HCV)

HIV-: HIV negative

HIV: human immunodeficiency virus

HVLT-R: Hopkins Verbal Learning Test-Revised

Imm: immediate

INSTI: integrase inhibitors

LPA: Latent Profile Analysis

MND: mild neurocognitive disorder

MTL: medial temporal lobe

NC-AE: non-ART medications with known neurocognitively adverse effects

NNRTI: non-nucleoside reverse transcriptase inhibitors

NRTI: nucleoside reverse transcriptase inhibitors

PHQ-9: Patient Health Questionnaire-9

PI: protease inhibitors

PWH: people living with HIV

QoL: quality of life

RAVLT: Rey Auditory Verbal Learning Test

RCF: Rey Complex Figure

RFA: Radom Forest Analysis

SAC: Southern Alberta Clinic

SDMT: Symbol Digit Modalities Test

SMOTE: Synthetic Minority Over-sampling Technique

SQV: saquinavir

TMT: Trails-Making Test

WAIS-III: Wechsler Adult Intelligence Scale

WCST: Wisconsin Card Sorting Test

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1. INTRODUCTION

1.1. The Human Immunodeficiency Virus (HIV)

The Human Immunodeficiency Virus (HIV) is an infectious disease that attacks CD4+ T-lymphocyte cells (CD4 cells), effectively weakening the immune system and severely impairing the host's ability to fight infection and disease (WHO, 2019a). The virus is transmitted through one of five bodily fluids: blood, semen, pre-seminal fluid, rectal fluid, vaginal fluid, and breast milk (Butters et al., 1990). The most common methods of HIV transmission are through anal sex, vaginal sex, or the sharing of drug injection equipment. Behaviors such as having unprotected anal or vaginal sex, sharing contaminated needles, receiving unsafe blood transfusions, tissue transplantation and unsterile cuttings or piercings, as well as having other sexually transmitted infections puts individuals at greater risk of contracting HIV (WHO, 2019a). Left untreated, HIV can lead to Acquired Immunodeficiency Syndrome (AIDS), a life threatening disease characterized by various opportunistic infections and a depleted CD4 cell count. Globally, there are around 38 million people living with HIV (PWH) at the current time, including over 62,000 Canadians (WHO, 2019a). In Canada, there were 2,122 new cases of HIV infection reported in 2019 (Haddad, Weeks, Robert, & Totten, 2021). Males accounted for 69.8% of these cases, with men between 30 and 39 years of age having the highest rate of new infections (16.8/100,000 population). Although there is no cure for HIV, effective treatment has rendered the disease a chronic but manageable illness with most treated PWH having similar life expectancies as people who are HIV negative (HIV-) (van Sighem et al., 2010).

1.2. HIV treatment

Advancements in HIV research have resulted in the change of the prognosis of HIV from a guaranteed death sentence to a chronic but manageable disease (van Sighem et al., 2010). One of the most notable achievements in HIV research is the discovery of modern antiretroviral therapies (ART) also called combination-ART (cART) in the mid-1990s. The drugs included in cART are molecular compounds that attack different aspects of the viral lifecycle, thereby significantly suppressing viral replication and preventing severe immunosuppression, essentially rendering HIV a severe but non-lethal, chronic condition (Arts & Hazuda, 2012). Major classes of ART consist of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), and fusion inhibitors (Arts & Hazuda, 2012). Less commonly used are CCR5 antagonists (e.g., maraviroc) and monoclonal antibodies (e.g., ibalizumab-uiyk) (Maeda, Das, Kobayakawa, Tamamura, & Takeuchi, 2019). Each class of ART acts on a specific step in the HIV life cycle to inhibit the replication of the virus (Figure 1).

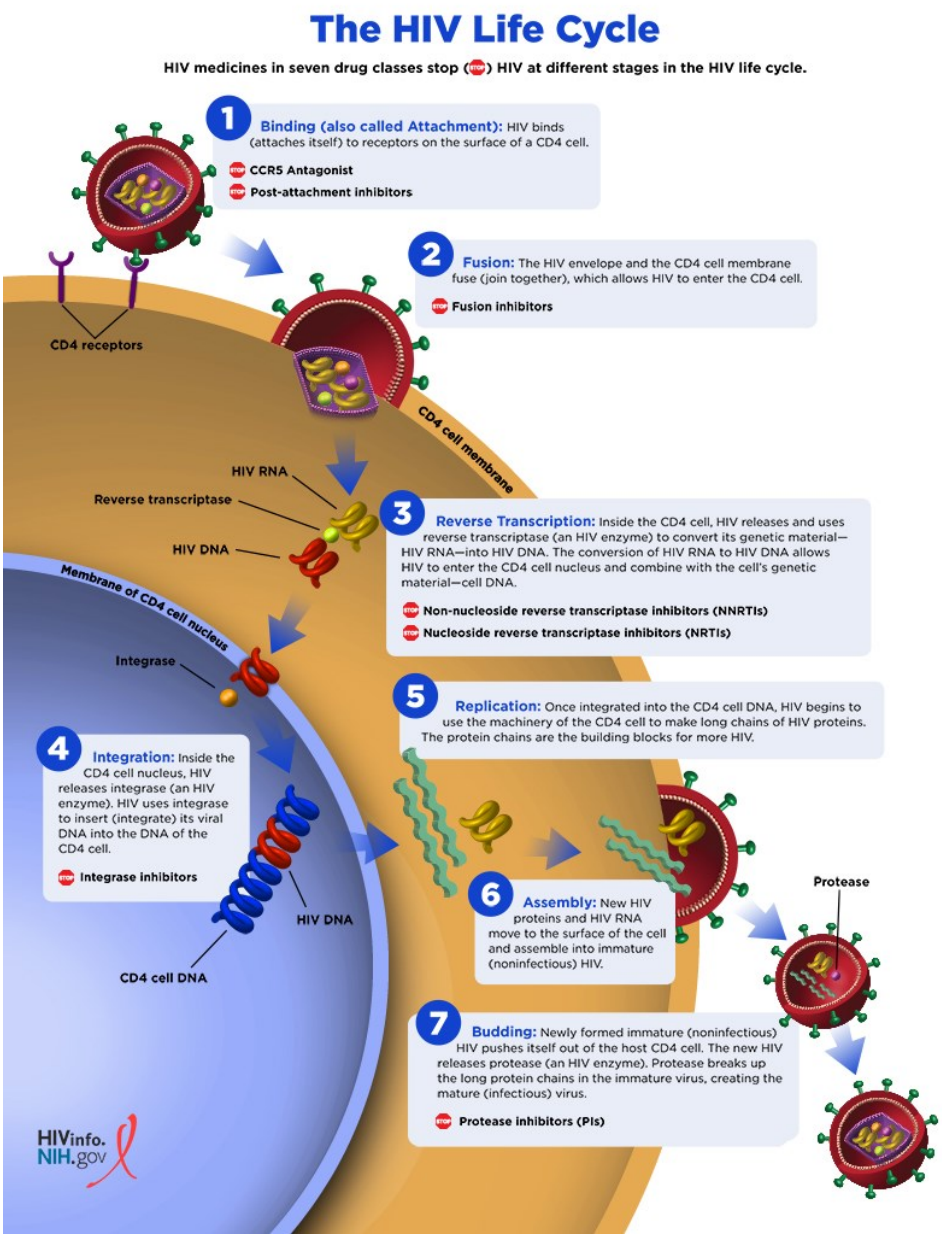


Figure 1. Life Cycle of HIV (US Department of Health Services, image retrieved from https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle

Viral entry is the target step of fusion inhibitors and the less commonly used chemokine receptor antagonists. NRTIs and NNRTIs inhibit reverse transcriptase, an enzyme that allows HIV RNA to alter the DNA of CD4 cells. Integrase inhibitors target replication through hindering the

integration of newly transcribed HIV DNA into the host DNA. Finally, protease inhibitors target the last step of the cycle, preventing the conversion of immature non-infectious HIV into mature infectious HIV.

Over the past two decades the rate of HIV-related deaths has decreased by 51% which is in large part due to the introduction of cART and the result of efforts by various HIV programmes increasing access to testing and treatment (WHO, 2019a). As of July 2020, 26 million PWH (68.4% of PWH) were receiving antiretroviral therapy with 59% of PWH globally achieving successful viral suppression with no risk of infecting others (WHO, 2019a). This treatment rate marks a 2.4% increase from the estimated 25.4 million PWH receiving treatment at the end of 2019. However, it is only half of the increase seen between January and June of 2019 (4.8%). It is likely that the number of PWH starting treatment later in 2019 is lower due to a reduction in HIV-testing, cART initiation, and treatment disruptions as a result of the COVID-19 pandemic. For instance, a South African study investigating the effect of the 2020 South African COVID-19 lockdown on HIV testing and treatment found that while cART provisions were generally maintained during the lockdown, HIV testing and cART initiations were heavily impacted (Dorward et al., 2021). In fact, the study suggests that since the first week of the lockdown (beginning on March 27th, 2020) there was an estimated 46.2% decrease in cART initiations. However, there was gradual improvement of cART initiation rates over the next 3 months (April 2020 – July 2020), approaching pre-lockdown levels. Likewise, the World Health Organization reports that by December 2020 testing and treatment rates had shown steady recovery.

Treatment strategies have changed drastically since the start of the HIV/AIDs epidemic. Early in the epidemic there were very few pharmacological treatments for PWH. Treatment was

primarily focused on preventative measures against common pathogens and the management of illnesses related to HIV-infection (Arts & Hazuda, 2012). In 1987, the NRTI zidovudine (also known as azidothymidine, AZT) became the first approved antiretroviral drug to treat HIV. During this time, ART was given as monotherapy with patients taking one medication at a time. The limitations of a single-drug treatment regimen quickly became evident. Although evidence indicated a greater survival rate at 24 weeks of treatment, by week 48 on the medication these survival benefits has vanished (Hamilton et al., 1992). Individuals receiving AZT alone developed very rapidly developed AZT-resistant strains of the virus (Larder, Darby, & Richman, 1989). In an effort to combat this, dual therapy (regimens containing two different medications) was introduced in 1993. Unfortunately, dual therapy would also have largely time-limited effects as a result of rapid drug resistance development (Lorenzi et al., 1999). It was not until after the FDA approval of saquinavir (SQV), the first protease inhibitor, in late 1995 that a new drug regimen capable of combating the pitfalls of prior ART regimen strategies was introduced (Baker, 1995). Combination ART (cART), or modern ART, is a cocktail of 3 or more different antiretroviral drugs and differs from its predecessors by combining at least two different molecular targets to attack the HIV-life cycle, which in turn decreases the risk of developing drug resistance. This treatment strategy has proven highly efficacious at decreasing viral load, often to undetectable amounts, and has completely revolutionized HIV treatment, remaining the preferred treatment approach since its introduction in 1996 (WHO, 2019a).

1.3. CNS effects of HIV

HIV infection has multiple potential effects in the CNS, including neuropathological, anatomical and downstream neurocognitive impacts. As early as 15 days after primary infection, HIV penetrates the blood-brain-barrier (BBB) via migrating myeloid and lymphoid cells (Ellis,

Calero, & Stockin, 2009). In this process, aptly coined the "Trojan Horse", HIV-infected monocytes and T-cells cross the BBB and release the virus into the central nervous system (CNS) (Davis et al., 1992). Once in the brain, free virions infect brain macrophages, microglia, and astrocytes, leading to a cascade of effects that can alter the brain's integrity and subsequently lead to neurological disorders, including neurocognitive impairment. Inflammatory processes initiated through the activation of both infected and uninfected microglia (in response to viral replication) and astrogliosis (due to the infection of astrocytes) lead to synapto-dendritic dysfunction, neuronal loss, microglial nodules, gliosis, myelin pallor, multinucleated giant cells, and the disruption of neural functioning (Hazleton, Berman, & Eugenin, 2010; H. Liu, Xu, Liu, & Xiong, 2016; Ortega, Brier, & Ances, 2015), even though HIV does not directly infect neurons or oligodendrocytes (H. Liu et al., 2016). Brain changes and downstream neurocognitive changes may occur in HIV infection as a result of these processes. Early anatomical studies reported decreased volumes in subcortical brain regions, especially the basal ganglia (Aylward et al., 1995; Aylward et al., 1993; Berger & Arendt, 2000). Prior to the introduction of cART, changes in brain macro- and micro-structure were largely due to HIV encephalitis and opportunistic infections (Levy & Bredesen, 1988). Although cART has decreased the incidence of these opportunistic infections, HIV effects on brain structure in cART-treated PWH continue to occur (O'Connor, Jaillard, Renard, & Zeffiro, 2017). While some studies report decreases in total brain volume (Di Sclafani et al., 1997), an indicator of global atrophy, newer studies reported little or no differences in global brain volume relative to controls, perhaps suggesting that faster initiation of ART after primary infection may decrease the risk of whole-brain atrophy (O'Connor et al., 2017; Ragin et al., 2012; Thompson et al., 2006). If observed, both subcortical and cortical gray matter in multiple regions can be affected, including the left inferior frontal gyrus, left superior

temporal gyrus, anterior cingulum, occipital lobe, and inferior parietal lobe (Lewis-de Los Angeles et al., 2017; J. Li et al., 2018; Y. Li, Li, Gao, Yuan, & Zhao, 2014; D. Liu et al., 2020). Analysis of cortical thickness in PWH in comparison to HIV-negative controls also pointed to cortical thinning in the frontal, parietal, and temporal lobes, with a 15% decrease in primary sensory, motor, and premotor cortex (Thompson et al., 2005). In 92 aviremic PWH, Sanford, Fellows, Ances, and Collins (2018) observed reduced cortical thickness in bilateral primary sensory and motor cortex, superior temporal gyrus and poles, middle and posterior cingulate cortex, and left frontal lobe. Reduced cortical thickness in these regions were accompanied by smaller subcortical gray and white matter volumes in the thalamus, caudate, putamen, globus pallidus, brainstem, and midbrain. White matter reductions as a result of HIV infection can be visible in larger structures like the corpus callosum, bilateral external capsule and mid cerebral peduncles (Sarma et al., 2014), but evidence also comes from diffusion tensor imaging studies suggesting diffuse white matter changes in HIV affecting cortical and in subcortical brain regions (Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007; Pomara, Crandall, Choi, Johnson, & Lim, 2001; Thurnher et al., 2005; Wright et al., 2015; Zhu et al., 2013). The latter DTI studies reported decreased fractional anisotropy and increased mean diffusivity which may indicate reduced axonal myelination and degeneration (Alexander, Lee, Lazar, & Field, 2007) of white matter tracts in PWH. Functional changes in the brain have also been observed in HIV. For example, in medial temporal lobe (MTL) regions fMRI changes were observed in PWH and related to memory changes. Maki et al. (2009) tested a female-only cohort of 54 PWH and 12 controls (Maki et al., 2009) during encoding and 20-minute delayed recognition of a block design memory task used in the Baltimore Longitudinal Study of Aging (Beason-Held, Golski, Kraut, Esposito, & Resnick, 2005) adapted specifically for the fMRI environment. Results

showed decreased activation in parahippocampal gyrus and hippocampus during encoding, particularly in the left hemisphere in HIV+ women relative to controls, accompanied by an increase in hippocampal activation during delayed recognition of the study materials. Further analysis found that higher BOLD response in the left hippocampus during encoding was associated with better performance in verbal memory assessed with the HVLT administered outside the scanner, whereas higher signal intensity in the right hippocampus during delayed recognition was associated with poorer performance on the HVLT. These results suggest changed functional patterns (hypo- and hyperactivation) in PWH in the MTL structures during memory formation/retrieval, with implications to neuropsychological deficits in clinical memory tests. A recent study using resting-state functional MRI by Yang et al. (2021) in 99 PWH tested the relationship between memory (HVLT-retention), functional connectivity within the medial temporal-frontal circuitry typically involved in memory processes and Apolipoprotein status (e4). The authors reported an interesting set of findings where Apolipoprotein ε4 was associated with worse memory performance and reduced functional connectivity in the memory network (which was anatomically altered to be focused on the caudate rather than the hippocampus). While reduced functional connectivity in the memory network was linked to lower CD4+ nadir count, this was only the case in ε4 carriers. Vice versa, effects of ε4 on memory performance were mediated through memory network functional connectivity, but only when CD4+ cell count nadir was low. Thus, in some PWH (i.e., those with Apolipoprotein ε4 status, exacerbated by legacy effects of severe past immunosuppression), reduced functional connectivity in memory circuits may be related to lowered memory performance.

If present, neurocognitive impairment in HIV, currently still referred to as HIV-associated neurocognitive disorders (HAND) (Antinori et al., 2007), is characterized by

impairment in neuropsychological domains including executive functions, memory, motor functions, information processing speed and attention (Heaton et al., 2011; Woods, Moore, Weber, & Grant, 2009). HAND is among the most prevalent comorbidities of HIV and the current consensus (or "Frascati') criteria by Antinori et al. (2007) provide a set of standards for the detection and staging of functional decline due to neurocognitive problems. These criteria classify HAND into one of three presentations: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). While the introduction of cART has decreased the prevalence of severe forms of HAND like HAD, the prevalence of less severe manifestations of HAND (ANI and MND) have increased (Ellis et al., 1997; Heaton et al., 2011). As current ART regimens effectively suppress HIV, the causes of persisting forms of less severe HAND, like ANI and MND, are difficult to interpret (Nightingale et al., 2021; Nightingale et al., 2014).

Requirements for the successful application of the Frascati criteria include the systematic evaluation of at least five different neuropsychological domains, the assessment of impairment in everyday functioning and the exclusion of other pre-existing conditions that may cause cognitive impairment, e.g., comorbid substance use and major depression (Table 1) (Antinori et al., 2007; Bearden & Meyer, 2016; Wei et al., 2020).

Table 1: Abbreviated summary of the Frascati-criteria (Antinori et al., 2007) for HIV-associated Neurocognitive Disorders (HAND), adopted from (Gisslen, Price, & Nilsson, 2011)

HAND class	Criteria
ANI	**HIV-associated asymptomatic neurocognitive impairment** • Cognitive impairment (performance of at least 1 SD below the mean for norms) involving at least two cognitive domains (language, attention/WM, executive function, memory, speed of information processing, perceptual-sensory, motor) • The cognitive impairment does not interfere with everyday functioning • No evidence of pre-existing cause, other than HIV, of the ANI
MND	**HIV-associated mild neurocognitive disorder** • Cognitive impairment (performance of at least 1 SD below the mean for norms) involving at least two cognitive domains (language, attention/WM, executive function, memory, speed of information processing, perceptual-sensory, motor) • The cognitive impairment causes mild disruption of daily activity (reported either by self report or by observation of others) • Criteria for delirium or dementia not met by the cognitive impairment • No evidence of pre-existing cause, other than HIV, of the MND
HAD	**HIV-associated dementia** • Marked cognitive impairment involving at least two cognitive domains (performance of at least 2 SD below the mean for norms on neuropsychological tests) • The cognitive impairment causes marked disruption of daily activity • Criteria for delirium not met by the cognitive impairment, and if met diagnosis of dementia must have been made prior in examination where delirium was not present

- No evidence of a pre-existing cause, other than HIV, for the dementia

While the Frascati criteria address limitations of scales that had previously been used to evaluate neurocognitive impairments in PWH (i.e., the Memorial Sloan Kettering Scale (Price & Brew, 1988) and American Academy of Neurology (AAN) criteria ("Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force," 1991), there are rising concerns about the diagnosis of HAND with these criteria (Bearden & Meyer, 2016; Nightingale et al., 2021; Tierney et al., 2017). For example, heterogeneity in neuropsychological test batteries and difference in normative control groups across studies (Kamminga, Cysique, Lu, Batchelor, & Brew, 2013; Mind Exchange Working, 2013; Valcour, Paul, Chiao, Wendelken, & Miller, 2011) have resulted in very large ranges of "HAND" cases in published cohort data (e.g., from 20% to 69% according to a review of studies by Nightingale et al. (2014). Some studies (e.g., Underwood et al. (2018) suggested much lower rates, ascribing neurocognitive deficits in cART-treated individuals largely to comorbidities, demographic, and lifestyle factors, rather than HIV itself. A new framework for the diagnosis of cognitive impairment in HIV acknowledging the increasing effects of such factors, partly due to more wide-spread viral suppression with cART, has been proposed recently, emphasizing clinical assessments to better rule in- or rule-out causes for neurocognitive deficits apart from HIV (Nightingale et al., 2021). In this framework, Nightingale et al. (2021) suggest eliminating ANI, the least severe form of HAND which is solely based on below-normative performance in neuropsychological tests but does not require the presence of functional impairment in daily life. Instead of using performance in neuropsychological tests in comparison to HIV- controls, the

authors suggest assessing the severity of cognitive impairment based on clinical history. Although further discussion of the feasibility and usefulness of such approach is beyond the scope of this thesis, a summary of the key differences between the Frascati criteria and the proposed novel framework can be found in Table 2. Owing to the ongoing discussion and ambiguity of ascribing etiology to neurocognitive deficits if observed in PWH, the "HAND" term will not be used in the current thesis.

Table 2: Summary of the key differences between Frascati criteria (Antinori et al., 2007) and this new proposed framework (Nightingale et al., 2021)

	HAND: Existing Criteria	**Cognitive Impairment in PWH: Proposed New Framework**
Definition	A cognitive disorder caused by the direct effect of HIV on the brain	Symptomatic cognitive impairment from any cause in a persons living with HIV
Proportion with asymptomatic impairment	Most	None
Diagnosis	Based on performance on cognitive tests compared to matched controls	Based on clinical history, including observer account where possible
Low cognitive test performance without symptoms	Termed ANI, which is part of HAND and hence labeled a cognitive disorder	Described as "low performance on cognitive tests," which is not part of cognitive impairment
Comorbidities	Divided into confounding (not HAND) and contributing	Comorbid factors specified alongside relative

	contribution of HIV brain disease

1.4. CNS effects of ART on cognition in PWH

The pathogenesis of neurocognitive deficits in HIV is multifactorial and includes host factors (severe past immunosuppression, genetic factors), treatment-related factors (ART effectiveness/CNS-penetrance, adherence, toxicity), as well as demographic and comorbidity-related factors (sex; age; education; age-related comorbidities: cardiovascular disorders, diabetes, metabolic disorders; psychiatric comorbidities), as outlined in Figure 2 (Nightingale et al., 2014).

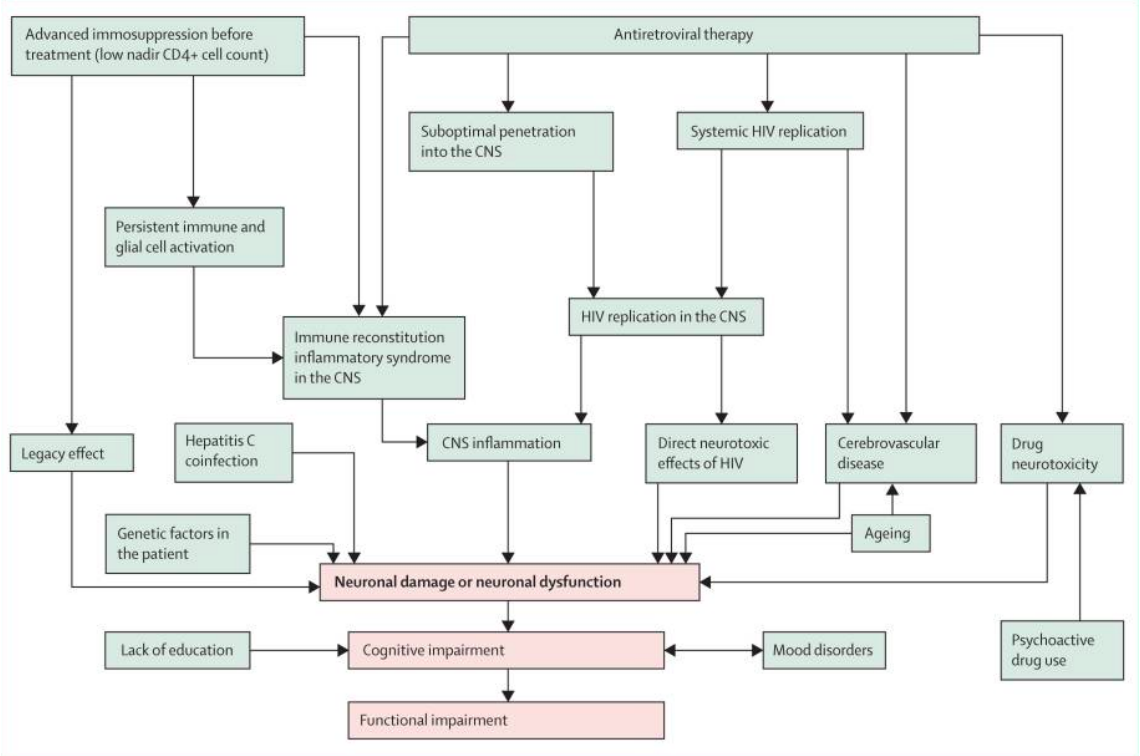


Figure 2. Overview of proposed pathological mechanisms underlying HIV-associated neurocognitive disorders (Figure 2 from Nightingale et al., 2014)

Among the most used measures is the CNS penetrance effectiveness (CPE) score. CPE is a ranking system created by Letendre et al. (2008), and updated by Letendre (2011), to compare the CNS penetrance of each ART. A higher CPE score then is interpreted as higher penetrance of that ART into the brain. Although CPE is widely used in the literature as a metric to estimate ART CNS-efficacy, there are complications with this ranking that can obscure true relationships to the assumed downstream neurological damage and neurocognitive changes. For instance, the strength of experimental evidence used to derive the initial CNS penetrance scores of individual ARTs was variable and rather qualitative. In addition, most of the evidence came from animal studies, limiting interpretation in humans. Most of the literature used to construct CPE ranks reported on levels of ART within CSF using lumbar punctures. Although concentrations of ART in the CSF can mimic concentrations of ART in the brain better than those in the plasma, the fact remains that drug levels in the CSF do not necessarily equate brain levels (Pardridge, 2011). For example, ART levels in the CSF can exceed concentrations in brain tissue (Brewster et al., 1997). Finally, multiple newer drugs are not included in the CPE. Due to these issues within the CPE ranking system, it is important to explore the possible impact of ARTs independent of the use of CPE. While CPE provides an approximate method to estimate ART effectiveness in the CNS, the most direct way to investigate ART concentrations and efficacy within the brain remains through the analysis of brain tissue. As previously discussed, the virus is able to enter the brain by infecting immune cells that are able to cross the BBB. However, no such mechanism exists for ARTs. As such, brain-targeting efficiency of ARTs is quite low. Asahchop et al., (2017) found the EC50 (half-maximal effective concentration) values for specific ART drugs in human HIV-infected cells in the CNS (microglia) was much higher compared to cells within the periphery (bone-marrow derived macrophages and peripheral blood mononuclear cells).

Likewise, in-vivo concentrations of ART medications were found in the range of 10 to 100-fold less within brain tissue in comparison to liver and plasma levels in mice. These findings confirm that ART are not as effective within the brain as they are within the periphery, which may be one of the many factors that contribute to the persistence of neurocognitive impairments in HIV.

In addition to *low* CNS penetrance of ART medications, long-term exposure and potential neuro*toxic* effects of ART could also be among the reasons for persistent neurocognitive problems in treated HIV (Shah et al., 2016), and there is evidence from several studies indicating that ART may have neurotoxic effects (Lanman, Letendre, Ma, Bang, & Ellis, 2021; Shah et al., 2016). For example, K. Robertson, Liner, and Meeker (2012) found therapeutic levels of several ART affected dendritic beading and pruning in rat neuronal tissues. Likewise, applications of the PIs ritonavir and lopinavir resulted in dose-dependent decreases in oligodendrocyte maturation (Jensen et al., 2015), an effect possibly mediated through cerebrovascular pathologies as observed in neuropathological studies in humans (Soontornniyomkij et al., 2014). Further evidence comes from Vivithanaporn, Asahchop, Acharjee, Baker, and Power (2016) reporting the PIs amprenavir and lopinavir applied at therapeutic concentrations to human astrocytes increased sensitivity to glutamate, which may lead to excitotoxicity and facilitate cell death (Dong et al., 2010). Specific INSTIs may also have neurotoxic effects. For instance, a study in primary rat neuroglial cultures demonstrated toxicity of elvitegravir, a relatively novel integrase inhibitor Stern et al. (2018). In a study by Latronico et al. (2018) The INSTI raltegravir (as well as the PI darunavir and least so, the CCR5 co-receptor antagonist maraviroc) when administered at higher than clinical concentrations induced the production of reactive oxygen species in primary cultures of rat astrocytes, suggesting that

oxidative stress may represent a mechanism of antiretroviral toxicity (see also Lanman et al. (2021) for a recent review).

A main target of ART is to stop the progression of HIV infection into AIDS which has been most definitively linked to severe forms of neurocognitive impairment (Cysique, Maruff, & Brew, 2006). However, studies suggest possible negative relationship between ART exposure and neurocognitive deficits in HIV (Cysique & Brew, 2009). The NNRTI efavirenz has been linked to worse cognitive performance in multiple epidemiological HIV studies (Ciccarelli et al., 2011; Ma et al., 2016; Rubin & Maki, 2019; Williams et al., 2021). For instance, Ma et al. (2016) compared cognitive performance between PWH who had received long-term (>12 weeks) efavirenz (n = 272) versus ritonavir-boosted lopinavir (n = 173) ART. Individuals receiving efavirenz performed significantly worse in verbal fluency, executive functions, speed of information processing, and working memory domains compared to participants on ritonavir-boosted lopinavir. Additionally, a higher proportion of individuals in the efavirenz group showed clinically substantial impairment (Global Deficit Scores ≥ 0.5) in information processing speed. Likewise, in an Italian cohort of 146 PWH, efavirenz use was found to be associated with an increased likelihood of HAND (Ciccarelli et al., 2011). Regarding PIs, Soontornniyomkij et al. (2014) found that PI-based ART regimens may be indirectly associated with an increased likelihood for HAND mediated through an increase in cardiovascular comorbidities, in this case, cerebral small vessel disease. O'Halloran et al. (2019) compared cognitive and brain changes in a cohort of 202 PWH who were either prescribed INSTI-based ART regimens at the time of neurocognitive testing or non-INSTI-based ART regimens. Individuals with INSTI-based regimens showed higher rates of cognitive impairment (Global Deficit Scores; (Carey, Woods, Gonzalez, et al., 2004), specifically, deficits in learning and memory. O'Halloran also reported

brain volume decreases in frontal, brain stem and cerebellar regions in INSTI-users compared to non-INSTI users. These findings suggest that (specific) types or classes of ARTs may have a negative influence on cognition.

Several ART medications may also be linked to neuropsychiatric complications, suggesting potential adverse CNS-effects. Efavirenz has long been characterized by neuropsychiatric outcomes in some PWH (Arendt, de Nocker, von Giesen, & Nolting, 2007; Kenedi & Goforth, 2011), including symptoms like dizziness, confusion, lethargy, impaired concentration, hallucinations and insomnia (Cavalcante et al., 2010). It is estimated that up to 50% of PWH who receive efavirenz experience some form of negative neuropsychiatric outcome (Gaida, Truter, Grobler, Kotze, & Godman, 2016; Kenedi & Goforth, 2011). The INSTI raltegravir can temporarily cause mental health symptoms after treatment initiation (e.g., insomnia, nightmares, depressive symptoms, psychotic symptoms; (Eiden, Peyriere, Peytavin, & Reynes, 2011). Neuropsychiatric symptoms were the most common reason for discontinuation of treatment with INSTI in another study (Penafiel et al., 2017). The INSTI dolutegravir has also been linked to higher rates of neuropsychiatric symptoms Hoffmann et al. (2017), especially in older individuals. These results are of particular importance, as dolutegravir based regimens are the recommended first-line treatment for HIV in adults, adolescents and infants while raltegravir is the preferred first-line treatment in neonates (WHO, 2019b). Given that ARTs are a mandatory life-long treatment for PWH, it is imperative to elucidate their potential role in neurocognitive problems.

1.5. Neurocognitive functions in treated HIV

As already alluded to, neurocognitive functions in PWH from the pre- and post-cART eras have changed (Cysique, Maruff, & Brew, 2004; Heaton et al., 2011)from a primarily subcortical impairment of dominant motor dysfunction (including extrapyramidal signs such as rigidity, tremor, and bradykinesia) and psychomotor slowing, with some differences depending on presence or absence of AIDS (Cysique et al., 2006) to more milder, diffuse cortical profiles of impairment in cART-treated patients (Sacktor, 2018). The change in the neuropsychological profiles after introduction of cART has also been reflected in changes to the nomenclatures for these impairments. In 1991, prior to the introduction of cART, a group of neurologists, neuropsychologists, psychiatrists, and sociologists published definitions to aid in the diagnosis of HIV-associated cognitive impairment. Two terms were developed, minor cognitive motor disorder and HIV-associated dementia ("Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force," 1991). Given the predominantly subcortical pattern of brain involvement and associated neurocognitive impairments at the time, these earlier criteria focused on behavioral, affective, and motor abnormalities. A decade later, in the cART era, the Frascati criteria (Antinori et al., 2007) eliminated diagnoses on the basis of non-cognitive, neuropsychiatric/-behavioural changes (i.e., changes in mood and personality) and motor dysfunctions, indicating that the phenotype had changed. Instead, the Frascati criteria emphasized that neurocognitive disturbances became the more essential feature of neurocognitive impairment in treated HIV.

The changes in impairment patterns may have become apparent because not all aspects of cognition uniformly improve with cART or they may even deteriorate. For instance, while

psychomotor slowing typically improves with cART, performance in cortical domains such as executive functions and memory may not (Ferrando et al., 1998; Suarez et al., 2001). Likewise, evidence suggests that in the post-cART era, performance in (some) cortical functions can be even *more* impaired than they were pre-cART (Cysique et al., 2004) such that specific domains should be examined separately. Walker & Brown (2018) recently reviewed the extant evidence on executive functions in PWH receiving cART (Walker & Brown, 2018). Results wer largely drawn from cross-sectional cohort studies and indicated that across several executive function domains (working memory, set shifting, inhibition, and decision-making), PWH performed significantly worse than their HIV-uninfected counterparts. However, there was insufficient information on specific ARTs or cART regimens such that the only extractable parameter addressing cART was the percentage of patients receiving these medications in each study, without usable information on exact regimens, individual drugs, or dosages and combinations. Using this parameter, the authors observed no significant association between the percentage of participants receiving ART and performance in any of the executive function domains. Thus, even though several subdomains of executive functions were observed to be impaired across multiple HIV cohorts receiving cART to variable degrees, the simple rates of cART treatment did not appear to influence these outcomes, and hence relationships between cART and executive functions in PWH remained unclear. Another unanswered question from this study refers to the fact that no longitudinal outcomes were extracted, i.e., studies that had examined possible changes in cognition (executive functions in this case) after cART-initiation. No such review articles exist for other neuropsychological phenotypes in the cART era, for example learning and memory. The current thesis contains two studies addressing the overarching question whether there is a relationship between cART and neurocognitive functions in PWH

with two studies, one empirical study using retrospective analysis of lifetime ART exposure and current neurocognitive status in a well-characterised cohort of PWH (study 1) and one systematic review addressing memory functions in the context of cART in published data from multiple HIV cohorts (study 2).

2. THESIS QUESTIONS AND HYPOTHESES

As outlined in the introduction, neurocognitive deficits continue to persist in PWH despite treatment with ART. As cART has been the preferred regimen for over 2 decades, we can now assess whether long-term exposure to cART is related to cognition in PWH receiving these medications. Although executive functions have been examined systematically in this context, memory problems, an important domain of neurocognitive deficits in treated HIV, have not been systematically reviewed. I conducted two studies to assess the associations between ARTs and neurocognitive functions in PWH. These studies addressed two questions:

1) Study 1: What is the relationship between cumulative ART exposure and neurocognitive performance in a well-characterized and -treated cohort of PWH. Working hypothesis: Longer exposure to ARTs is an important factor associated with worse neurocognitive function in PWH, despite multiple other causes for neurocognitive impairment in HIV.

2) Study 2: Is there a relationship between memory functions and ARTs in published outcomes from HIV cohorts receiving modern ARTs? Working hypothesis: There is a distinguishable role of cART in memory performance in treated HIV cohorts, while accommodating other factors that influence memory.

3. STUDY 1 - LIFETIME ANTIRETROVIRAL EXPOSURE AND NEUROCOGNITIVE IMPAIRMENT IN HIV

3.1. Introduction

The introduction of modern antiretroviral therapies (ART) in the mid-1990s has resulted in a drastic decrease in mortality and morbidity of persons living with HIV (PWH) (Danforth, Granich, Wiedeman, Baxi, & Padian, 2017). Although there is no cure for the disease, many individuals can successfully manage the infection through these medications (Danforth et al., 2017). Nonetheless, neurocognitive deficits can persist in PWH despite treatment with ART although the prevalence of neurocognitive impairment varies widely (Heaton et al., 2010). Several factors likely contribute to the persistence of neurocognitive impairment among PWH receiving suppressive ART, including disadvantageous socio-demographic factors, age-associated and neuropsychiatric comorbidities, as well as sustained low-level viral replication within the CNS despite treatment (Alford & Vera, 2018; Thakur et al., 2019). Long-term exposure and potential neurotoxic effects of ART itself could also be among the reasons for persistent neurocognitive problems in treated HIV (Heaton et al., 2011; Thakur et al., 2019).

Major classes of ART comprise nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), and fusion inhibitors (Arts & Hazuda, 2012). Less commonly used are CCR5 antagonists (e.g., maraviroc) and monoclonal antibodies (e.g., ibalizumab-uiyk) (Maeda et al., 2019). Multiple histopathological studies have demonstrated neurotoxic effects of at least some ART on CNS cells. For example, K. Robertson et al. (2012) found therapeutic levels of several ART affecting dendritic beading and pruning in rat neuronal tissues. Protease inhibitors like ritonavir and lopinavir were found to result in dose-dependent decreases in oligodendrocyte

maturation (Jensen et al., 2015), possibly through cerebrovascular pathologies as observed in neuropathological studies in humans (Soontornniyomkij et al., 2014). Furthermore, the NNRTI efavirenz has been linked to neuropsychiatric (Kenedi & Goforth, 2011) and cognitive outcomes in a number of epidemiological HIV studies (Ciccarelli et al., 2011; Ma et al., 2016; Rubin & Maki, 2019; Williams et al., 2021). We previously observed that among the most prominent predictors of neurocognitive impairment in PWH were higher CNS-penetrance effectiveness (CPE) scores (Letendre, 2011) of their ART regimens, suggesting the possibility that highly penetrant ART regimens could negatively affect neurocognitive functions in PWH (Gomez et al., 2019). However, evidence for links between CPE and cognition has been inconclusive, with previous reports of negative relationships (Marra et al., 2009), positive relationships (Vassallo et al., 2017), as well as studies reporting no relationship between CPE and cognition in HIV (Ciccarelli et al., 2011).

This study examined the association between cumulative ART exposure and neurocognitive function. Our working hypothesis was that, while accommodating for the multifactorial nature of neurocognitive impairment, longer exposure to ARTs would be among the most important factors associated with worse neurocognitive function in PWH.

3.2. Methods

3.2.1. Cohort

Participants were all HIV-seropositive and receiving ART at the Southern Alberta HIV Clinic (SAC) in Calgary, Alberta, Canada. SAC is an outpatient clinic that provides comprehensive free HIV care to all PWH living in southern Alberta (Asahchop et al., 2016; McCombe, Vivithanaporn, Gill, & Power, 2013). All participants were currently receiving ART

medications, had normal or corrected-to-normal vision and hearing, were fluent in English, at least 18 years of age and had achieved at minimum a Grade 9 education. Exclusions were the presence of severe psychiatric (e.g., schizophrenia) or neurological disorders (e.g. brain tumors, strokes, epilepsy), history of brain damage/traumatic brain injury with loss of consciousness (>5 minutes), and uncorrected vision or hearing impairments. The current study restricted the selection of participants to include only individuals who were born in North-America (Canada and the United States of America) due to the absence of appropriate normative data for first-generation immigrants to Canada. The biases that this creates regarding the interpretation of neuropsychological performance is illustrated in a previous study performed by our group (Gomez et al., 2019). Nevertheless, an overview of the entire cohort is included in the supplement (Table S2, see also an illustration of outcomes in Figure S3 and Figure S4). Of the current 343 participants, a subset of participants (n=283) were also included in the previous study as well (Gomez et al., 2019). Written informed consent was obtained from all participants. The study was approved by the University of Calgary, 112 Conjoint Health Research Ethics Board, CHREB13-0615.

3.2.2. Neuropsychological Test Battery

Neuropsychological testing (45–90 min) was conducted in a single session at SAC by a psychometrist, comprising ten test scores from eight tests. Attention and processing speed were assessed with the Symbol Digit Modalities Test (SDMT; (Smith, 1973)]; correct responses) and number sequencing (completion time) in the Trail Making Test 2 (TMT-2) from the Delis-Kaplan Executive Function System (D-KEFS; [(Delis, Kaplan, & Kramer, 2001); [Fine, Delis, and Holdnack (2011)]). Motor function was assessed with the dominant and non-dominant hand completion time of the Grooved Pegboard (GPB; (Trites, 1977)]; CNNS™ ; [Schretlen, Testa,

and Pearlson (2010)]). Memory was assessed with immediate (imm) and 25-minute delayed recall (del) of the Hopkins Verbal Learning Test (HVLT; [(Brandt & Benedict, 2001)], CNNS™; [Schretlen et al. (2010)]). Language functions were correct responses in the D-KEFS (Delis et al., 2001) letter fluency (FAS; [Mitrushina, Boone, Razani, and D'Elia (2005)]), and category fluency (animals; CNNS™; [Schretlen et al. (2010)]). Aspects of executive functions were tested with the 64-card version of the Wisconsin Card Sorting Test, using perseverative errors as the measure (WCST; [(Kongs, Thompson, Iverson, & Heaton, 2000)]), and letter-number-switching (completion time) from the D-KEFS Trail-Making Test-4 (TMT-4; [Fine et al. (2011). Performance was transformed into z-scaled standard scores based on published normative reference data, using age- and education-adjustments in all scores, as well as adjustments for sex where available (see Table S3 for details on the normative references used).

There are multiple ways to classify neurocognitive impairment in PWH including Global Deficit Scores (Carey, Woods, Gonzalez, et al., 2004) or Clinical Ratings ("Frascati criteria") counting impairment in two or more cognitive domains (Antinori et al., 2007). Methodological variability (e.g., differences in thresholds for impairment, number and types of cognitive domains, tests per domain, weighing of impairment, etc.) and low specificity (McDonnell et al., 2014; Wang et al., 2019) have led to debates in determination, staging, and phenotyping of neurocognitive impairment in HIV (Paul, 2019). Here we used Latent Profile Analysis, a mixture-modeling technique that can empirically identify distinct profiles of neurocognitive performance patterns without the need to define cognitive domains, impairment thresholds, or severity of deficits. In LPA, groups of individuals with similar performance pattern across all tests are clustered together and features of these clusters can then be compared. LPA has been previously used to profile neurocognitive functions in HIV (Molsberry et al., 2018), including by

our group (Gomez et al., 2019). Supplemental Figure S5 further illustrates how the neurocognitively impaired patients would distribute to an "impaired" subgroup of patients according to the alternative classification criteria.

3.2.3. Cohort clinical and demographic features

The demographic characteristics of the participants that were studied included: age (years), cognitive reserve (median-split based on combining years of education and performance in the WRAT-4 Reading subtest; (Patel et al., 2013), sex, employment, AIDS and detectable viral load at time of testing. Continuous clinical variables included: length of diagnosed HIV infection, recent CD4 T-cell count, and nadir CD4 T-cell count. Dichotomous (yes/no) clinical variables were self-reported substance use (>9 alcoholic drinks per week, marijuana use, crack/cocaine use and use of other illicit drugs), Hepatitis C Virus (HCV) co-infection, ART side effects, toxoplasma serostatus, metabolic disorders (lipodystrophy and dyslipidemia), diabetes, cardiovascular conditions (peripheral vascular diseases, myocardial ischemia, hypertension or infarction), psychiatric diagnoses (mainly mood and affective disorders) and self-reported presence of interpersonal violence. Two numerical self-report variables were also assessed: Patient Health Questionnaire-9 (PHQ-9; (Kroenke, Spitzer, & Williams, 2001) to assess depressive symptoms and health-related quality of life (QoL; (Crane et al., 2006) in the past month. In addition, we categorised all non-ART medications with known neurocognitively adverse effects (NC-AEs) using Radtke et al.'s (2018) classification scheme, in order to control for known effects of non-ART medication burden at the time of neurocognitive testing (Rubin et al. (2018).

3.2.4. Quantification of ART

History of ART from time of enrolment at SAC was obtained from medical records for each participant, as was the number of NC-AEs at test date. ART medication use was defined by all past class use i.e. NRTI, NNRTI, PI, and INSTI, omitting CCR5 antagonists (N=7) and fusion inhibitors (N=2) due to low prescription rates. As a measure of lifetime ART-exposure we calculated the total duration (in years) by ART class.

3.2.5. Statistical analyses

We first identified empiric neurocognitive profiles using Latent Profile Analysis (LPA) using Mplus 8.3 (Muthen & Muthen, 1998-2015), with the optimal number of profiles identified though Vuong-Lo-Mendell-Rubin Test (Vuong, 1989), Bootstrapped Likelihood Ratio Test (McLachlan G. J., 2000), Akaike's Information Criterion (AIC), and Bayesian Information Criterion (BIC). Secondly, the different LPA profiles were compared regarding cumulative ART-exposure, along with other demographic and clinical factors, using univariate χ^2-tests for dichotomous variables and ANOVA for continuous variables (non-parametric Kruskall-Wallis tests, if indicated), including post-hoc tests with multiple comparison correction.

In a third step, we used machine learning (Random Forest Analyses, RFA) to evaluate which patient characteristics predicted membership in the empiric neurocognitive profiles. We selected 26 predictors for the RFAs, including years of ART exposure by class as well as the total number of NC-AEs at the test date, and omitting predictors that were redundant or had frequencies of fewer than 5% in any of the LPA profiles. We had complete (gapless) ART history for 71% (N=243) of the participants. Of the remaining participants, the average gap

length in ART history was 13.1 months (+/- 29.3). For those with gaps in their ART history, lifetime exposure was conservatively calculated based on the available information, with no further imputation of missing ART data. We used conditional permutation accuracy importance (Strobl, Boulesteix, Kneib, Augustin, & Zeileis, 2008) to identify the important predictors, which allows combining dichotomous and numerical predictors, as well as moderate collinearity between predictors in order to evaluate the individual importance of each predictor, even if they are correlated (e.g., age, HIV duration, ART exposure duration). Following Strobl et al. (2009), the threshold for an important predictor was set by taking the absolute value of the lowest variable importance score obtained from each RFA. In order to avoid classification biases towards the majority class, Synthetic Minority Over-sampling Technique (SMOTE; (Chawla, Bowyer, Hall, & Kegelmeyer, 2002) was used when LPA profiles were very different in size. Parameters included an *ntree*-value of 5000 trees per RFA, and *mtry*=2 variables for splitting at each tree node. The directionality of important predictors was determined by inspecting the univariate outcomes. RFA was conducted in R (R Core Team 2018). Overall model strength was evaluated by area under the receiver operating curve (AUC) and F_1 scores (see also (Gomez et al., 2019). Since variable importance scores vary depending on the included predictors and as such, the numerical values of variable importance scores are not meaningful outside of that specific model, rank order of the predictors are provided as well, in order to illustrate the relative importance of each predictor within each analysis and to give some comparison across analyses.

For ART-classes emerging as important predictors, exposure durations of the individual drugs contained in the class were then examined, using analyses of covariance on exposure duration to the individual drugs between cognitive profiles, controlling for HIV duration.

Furthermore, we conducted partial correlations between exposure duration to the individual ARTs and performance in the neuropsychological test scores, again controlling for HIV duration.

3.3. Results

3.3.1. Neurocognitive profiles

Latent profile analysis on neurocognitive performance in the ten test scores showed a three-profile model with the best fit (Figure 3), similar to our previous findings in a subset of patients (Gomez et al., 2019). A high performing profile consisted of 132 (38.5%) participants, followed by an intermediately performing group of 152 (44.3%) participants with decreased performance, especially in memory, and a globally low performing profile in 59 (17.2%) participants. In the profile with low performance, scores ranged between one and two standard deviations below normative average (M=-1.33; Figure 3). Thus, the low performing profiles can be considered neurocognitively impaired.

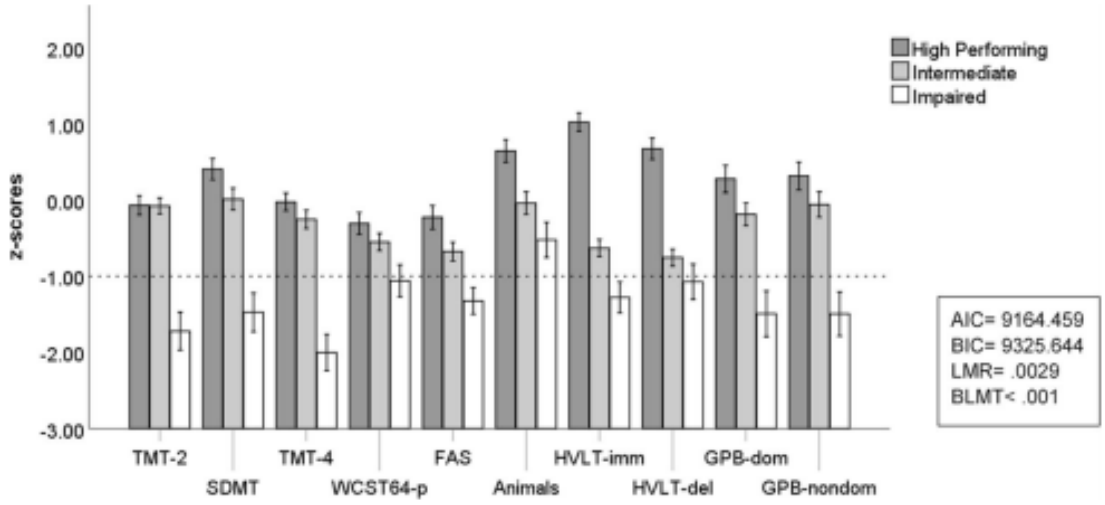


Figure 3. Latent Profile Analysis of 343 participants from the Southern Alberta HIV clinic. Bars represent means of the z-scaled performance in the ten individual neuropsychological test scores used to derive the profiles. Error bars are 95% confidence intervals.

AIC Akaike's information criterion, Animals Delis–Kaplan Executive Function System Category Fluency (animals), BIC Bayesian information criterion, BLRT bootstrapped likelihood ratio test (p value), FAS Delis–Kaplan Executive Function System Letter Fluency, GPB-dom Grooved Pegboard (dominant hand), GPB-nondom. Grooved Pegboard (non-dominant), HVLT del. Hopkins Verbal Learning Test (delayed), HVLT-imm. Hopkins Verbal Learning Test (immediate), LMR Vuong-Lo-MendellRubin likelihood ratio test (p value), SDMT Symbol Digit Modalities Test, TMT-2 Trail Making Test 2, TMT-4 Trail Making Test 4, WCST64-p Wisconsin Card Sorting Test 64-Card version, perseverative errors

3.3.2. Univariate differences between neurocognitive profiles

Table 3 lists the univariate differences between the three profiles. There was a significantly longer exposure duration to INSTI (and non-significantly, NNRTIs) in the impaired group, especially compared to the high performing group. Compared to one or both higher performing profiles, the neurocognitively impaired group was also older, reported lower QoL, had higher

rates of diabetes, higher rates of suicide risk, a higher number of NC-AEs at the time of test groups (see Table S1 for additional details on NC-AE), increased current depressive symptoms, higher rates of unemployment/retirement, higher rates of participants with Aboriginal/Metis background, and lower cognitive reserve.

Table 3: Participant characteristics and differences between LPA profiles (N = 343); data are means (SD), or medians (range), or percentages within profiles

Variable	High (n = 132)	Intermediate (n = 152)	Impaired (n = 59)	Test Statistic	p-value	RFA
Age (years)	46.8 (10.7)[a]	50.0 (10.4)[b]	52.0 (10.4)[c]	F(2,340)= 6.13	**.002**	X
Sex (male)	92.4%	89.5%	89.8%	$\chi^2(2)$= 0.79	.675	X
Employment (currently employed)	73.5%[a]	65.1%[a]	22.0%[b]	$\chi^2(2)$= 47.37	**<.001**	X
Education (years)	14.0 (2.4)	13.7 (2.6)	13.5 (2.8)	F(2,340)= 1.10	.335	
WRAT-Reading (IQ-scaled)	109.3 (11.9)[a]	102.0 (13.0)[b]	97.0 (15.9)[c]	F(2,322)= 20.10	**<.001**	
High cognitive reserve	65.1%[a]	40.6%[b]	37.5[b]	$\chi^2(2)$= 20.03	**<.001**	X
QoL (1 = poor, 5 = excellent) †	4.0 (1.0-5.0)	3.0 (1.0-5.0)	3.0 (1.0-5.0)	$\chi^2(2)$= 5.67	0.59	X
HIV duration (in years)	11.7 (8.4)	12.4 (8.1)	13.7 (8.8)	F(2,352)= 0.98	.375	X
Detectable VL	7.6%	11.8%	13.6%	$\chi^2(2)$= 2.081	.353	X
Recent CD4 T-cell (count/mm³)	566.8 (239.8)	572.5 (288.5)	528.0 (247.2)	F(2,340)= 0.63	.532	X

Variable	High (n = 132)	Intermediate (n = 152)	Impaired (n = 59)	Test Statistic	p-value	RFA
Nadir CD4 T-cell (count/mm³)	202.2 (156.0)	202.03 (162.9)	182.2 (173.5)	F(2,340)= 0.37	.692	X
AIDS (nadir < 200 count/mm³)	50.8%	49.3%	62.7%	$\chi^2(2)$= 3.22	.200	
ART non-adherence (last five days)	7.6%	9.2%	12.1%	$\chi^2(2)$= 0.96	.62	X
ART side-effects	16.7%	17.1%	13.6%	$\chi^2(2)$= 0.41	.82	X
Substance use						
Alcohol (binge)	3.8%	7.9%	5.1%	$\chi^2(2)$= 2.24	.32	
Marijuana	26.5%	38.8%	25.4%	$\chi^2(2)$= 6.26	**.04**	X
Crack/cocaine	9.1%	4.6%	8.5%	$\chi^2(2)$= 2.42	.30	X
HCV co-infection	3.8%	9.2%	10.2%	$\chi^2(2)$= 3.95	.14	
Toxoplasma seropositive	7.6%	7.2%	5.1%	$\chi^2(2)$= 0.41	.81	X
Metabolic disorders	31.1%	35.5%	33.9%	$\chi^2(2)$= 0.64	.73	X
Diabetes	5.3%[a]	8.6%[a,b]	16.9%[b]	$\chi^2(2)$= 6.94	**.03**	X
Cardiac conditions	14.4%	15.8%	13.6%	$\chi^2(2)$= 0.21	.90	X
Psychiatric disorder	31.8%	33.6%	49.2%	$\chi^2(2)$= 5.83	.05	X
Interpersonal violence	25.8%	34.9%	39.0%	$\chi^2(2)$= 4.26	.12	X

Variable	High (n = 132)	Intermediate (n = 152)	Impaired (n = 59)	Test Statistic	p-value	RFA
Suicide risk	13.6%[a]	15.8%[a]	39.0%[b]	$\chi^2(2)=$ 18.83	**<.001**	X
PHQ-9 [†]	4.0 (0.0-26.0)[a]	5.0 (0.0-26.0)[a,b]	9.0 (0.0-23.0)[b]	$\chi^2(2)=$ 9.39	**.01**	X
ART exposure duration (years)	8.3 (6.4)	9.0 (6.8)	10.1 (7.1)	F(2,340)= 1.47	.23	
NRTI exposure duration (years)	8.2 (6.4)	8.7 (6.6)	9.6 (6.6)	F(2,340)= 0.98	.38	X
NNRTI exposure duration (years)	6.0 (4.9)	7.2 (5.3)	8.1 (5.6)	F(2,236)= 2.55	.08	X
PI exposure duration (years)	5.9 (4.9)	5.1 (4.8)	6.4 (5.9)	F(2,215)= 1.26	.29	X
INSTI exposure duration (years)	1.3 (1.1)[a]	1.7 (1.8)[a,b]	2.5 (2.6)[b]	F(2,141)= 3.72	**.03**	X
Number of NC-AEs at test date	1.0 (1.0-5.0)	1.0 (1.0-6.0)	2.0 (1.0-6.0)	$\chi^2(2)=$ 2.49	0.29	**X**
One or more NC-AE (%)	14.4%[a]	23.7Thak%[a]	45.8%[b]	$\chi^2(2)=$ 22.06	**<.001**	

ART antiretroviral therapy, *HCV* hepatitis C virus, *INSTI* integrase inhibitors, *NA* not applicable, *NC-AE* non-ART medications with known neurocognitively adverse effects, *NRTI* nucleoside reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *PHQ-9* Patient Health Questionnaire-9, *PI* protease inhibitors, *QOL* quality of life, *VL* viral load, *WRAT-reading* Wide Range Achievement Test, version 4, Reading subtest

[†]Median (range)

[a,b,c] :Different letter superscripts denote significant differences between groups in Bonferroni-corrected post hoc tests ($p < 0.05$)

3.3.3. Multivariate differences: characteristics of the neurocognitively impaired group

RFA was implemented to identify the most important predictors of membership to the neurocognitively impaired group, compared to the other profiles. In total, 26 variables (see Table 3) were used in the RFAs, including years of exposure duration by ART class. The reason for excluding some of the predictors at this stage were redundancy (e.g., AIDS and nadir CD4 T-cell counts) or low frequencies in one or more of the profiles (e.g., less than 10% of the cohort had non-Caucasian ethnicity). The outcomes of the RFAs are shown in Figure 4 and Figure 5, restricting the illustration to variable importance values that passed the statistical threshold. The RFAs involving the impaired group showed good fits (high performing group versus impaired group: AUC=0.846, F_1=0.79; intermediate group versus impaired group: AUC=0.791, F_1=0.75). The RFA between the two larger groups with intermediate or high neurocognitive performance had a relatively poor fit (AUC=0.602, F_1= 0.44), suggesting that these two groups' characteristics were not reliably distinguishable; this comparison was not further pursued.

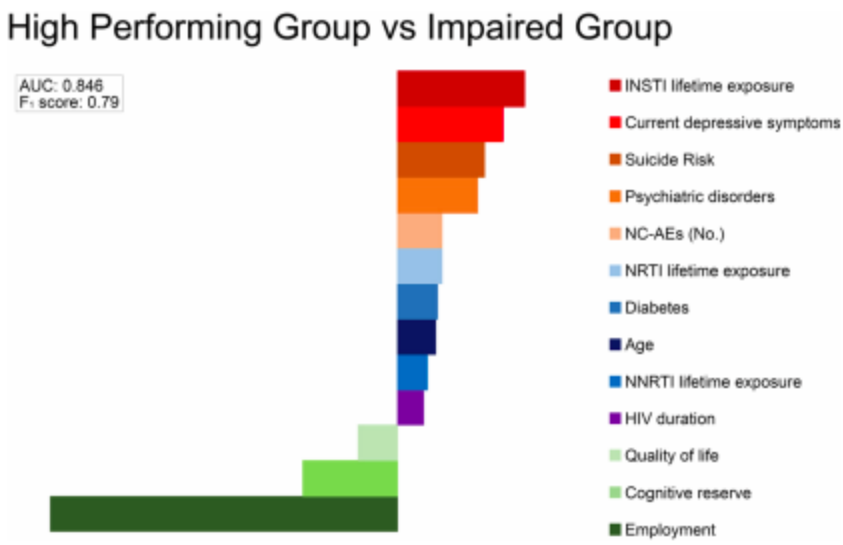


Figure 4. Random Forest Analysis comparing groups with high versus impaired neurocognitive performance. Direction of the bar corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis. INSTI integrase inhibitor, NC-AE non-ART medications with known neurocognitively adverse effects, NNRTI non-nucleoside reverse transcriptase inhibitor, NRTI nucleoside reverse transcriptase inhibitor, PI protease inhibitor

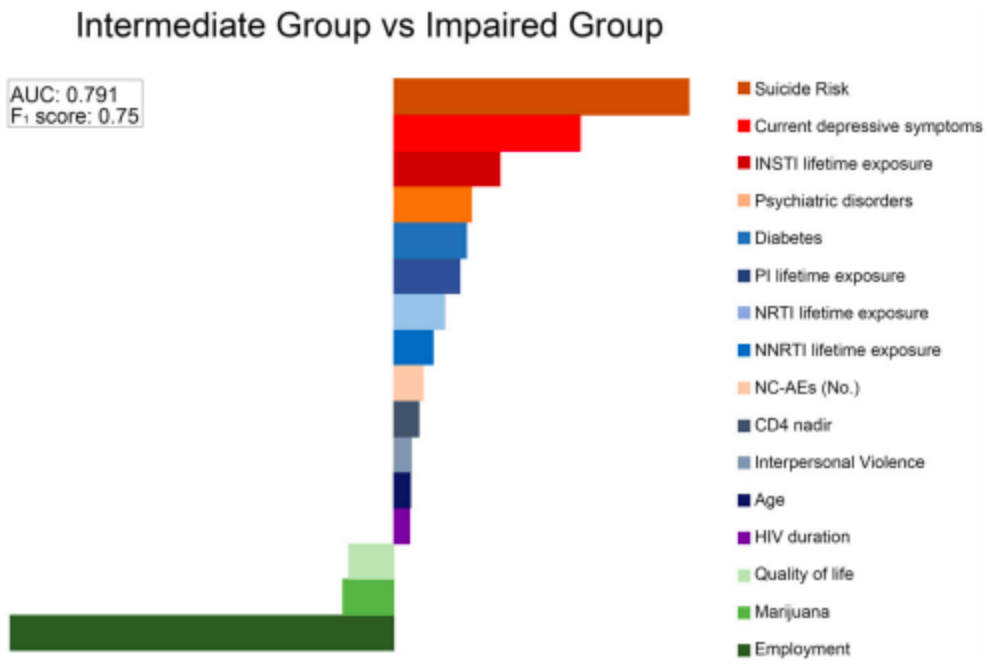


Figure 5. Random Forest Analysis comparing groups with high versus impaired neurocognitive performance. Direction of the bar corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis. For abbreviations, see Fig. 4.

Apart from unemployment/retirement, a longer duration of INSTI exposure was by far the most important ART-related predictor of placement into the neurocognitively impaired group compared to the high performing group (Figure 4). INSTI exposure duration was also among the most important variables distinguishing the impaired group from the group with intermediate neurocognitive performance (Figure 5). Membership in the lowest compared to both higher performing groups was also characterised by longer lifetime-exposure to NRTIs, NNRTIs, and PIs (compared to the intermediate group), although these effects much less important than INSTI exposure duration. Further characteristics of the impaired group compared to both other profiles

included older age and longer HIV duration, lower cognitive reserve, suicide risk (documented and self-reported past suicide attempts), psychiatric comorbidities, current depressive symptoms (PHQ-9), a higher number of NC-AEs, lower quality of life, and higher rates of diabetes. The impaired group was further differentiated from the intermediate group by lower nadir CD4 T-cell counts, lower rates of marijuana use, as well as higher rates of interpersonal violence (Figure 4, Figure 5).

In addition to the LPA-based profiles, we also conducted comparisons based on Global Deficit Scores of 0.5 or more to indicate neurocognitive impairment (Supplemental Figure 1) or based on Frascati-criteria with Clinical Ratings indicating impairment in at least two cognitive domains (Supplemental Figure 2). Both analyses had acceptable model fit scores (Global Deficit Scores: AUC= 0.83, F1-score= 0.70; Frascati-criteria; AUC: 0.84, F1 score: 0.74). As illustrated in Supplemental Figures 1 and 2, the important characteristics of neurocognitively impaired individuals in both of the analyses largely matched the current LPA-based results. A longer INSTI exposure duration was among the most prominent characteristics of neurocognitive impairment (GDS: rank 2 of 15; Frascati-criteria: rank 1 of 14), along with employment status, and followed by mental and physical health parameters.

3.3.4. Neurocognitive functions and specific integrase inhibitors

To explore the dominant role of INSTI exposure in neurocognitive impairment further, we examined the individual drugs included in the INSTI class. A total of 65 participants had a history of exposure to dolutegravir, 61 participants had taken raltegravir, and 38 participants were prescribed boosted elvitegravir, with 20 participants having had exposure to more than one INSTI. Among these and controlling for HIV duration, only dolutegravir exposure duration

significantly differed between profiles ($F(2, 60)= 4.85$, $p= 0.01$), with the impaired group having a longer dolutegravir exposure ($M= 2.84 \pm 2.62$ years), compared to the high performing group ($M= 0.90 \pm 0.66$ years, $p= 0.012$), with a similar trend compared to the intermediate group ($M= 1.54 \pm 1.66$ years, $p= 0.063$). Irrespective of the profiles, partial correlations controlling for HIV duration showed that dolutegravir exposure was negatively related to memory performance (HVLT imm, r=-.269, p=.033) and motor functions (GPB dominant, r=-.350, p=.005; non-dominant, r=-.289, p=.022). Raltegravir exposure was negatively correlated to letter-number switching (TMT-4, r=-.255, p=.049), an executive function test. Relationships between elvitegravir exposure and neurocognitive performance were not significant.

In summary, of the four major ART classes tested here, a longer duration of INSTI exposure was a prominent characteristic of a neurocognitively impaired group. Specifically, exposure duration to dolutegravir was longer in participants with impaired neurocognitive performance. In the entire cohort, longer dolutegravir exposure correlated to lower motor and memory functions, while raltegravir exposure duration was marginally linked lower cognitive flexibility.

3.4. Discussion

We identified three empiric profiles of neurocognitive performance patterns in our single-site cohort of 343 PWH. Two of the profiles were characterized by high or intermediate neurocognitive performance levels falling within normal ranges, although with lowered memory performance in the intermediate group. While machine learning could not reliably differentiate the two higher performing profiles, the third profile (N= 59 PWH, 17.2% of the total) was characterised by impaired neurocognitive performance and it was clearly distinguishable through both univariate analyses and machine learning. Apart from to-be-expected characteristics of the

low performing profile (higher rates of unemployment/retirement, older age, higher rates of ethnic minorities, lower QoL, lower cognitive reserve, higher rates of psychiatric comorbidities, diabetes, and a higher number of NC-AEs), multiple ART-related variables emerged as distinguishing features, with a longer lifetime exposure to INSTIs being among the most important predictors overall. Inspecting links between cognition and exposure to the three types of INSTIs in this cohort, the impaired group had longer cumulative exposure to dolutegravir in particular, and in the entire cohort, dolutegravir exposure duration was linked to motor functions and to memory.

Certain INSTIs have been associated with higher frequencies of neuropsychiatric symptoms, suggesting potential adverse CNS-effects, although these outcomes may covary with other risk factors (Williams et al., 2021). For instance, raltegravir can temporarily worsen mental health symptoms after onset of treatment (e.g., insomnia, nightmares, depressive symptoms, psychotic symptoms; (Eiden et al., 2011; Harris, Larsen, & Montaner, 2008). Neuropsychiatric symptoms were the most common reason for discontinuation of treatment with INSTI in another study (Penafiel et al., 2017). Dolutegravir has been linked to higher rates of adverse neuropsychiatric symptoms (Hoffmann et al., 2017), especially in older individuals. (O'Halloran et al., 2019) recently compared cognitive and brain changes in a cohort of 202 PWH who were either prescribed INSTI-based ART regimens at the time of neurocognitive testing or non-INSTI-based ART regimens. Individuals with INSTI-based regimens showed higher rates of cognitive impairment (Global Deficit Scores), specifically, deficits in learning and memory tests. O'Halloran also reported brain volumetric decreases in frontal, brain stem and cerebellar volumes in INSTI-users compared to non-INSTI users. Although we did not examine brain volume changes here, we observed that lifetime dolutegravir exposure was most strongly

associated with lower motor functions, i.e., functions that would typically be associated with the frontal-subcortical/cerebellar volume changes reported in O'Halloran et al. (2019).

The mechanisms through which INSTIs might affect neurocognitive functions are unclear but include both direct and indirect effects. A recent study in primary rat neuroglial cultures demonstrated neurotoxicity of elvitegravir but neither raltegravir nor dolutegravir (Stern et al., 2018). Conversely, Latronico et al. (2018) reported that raltegravir (as well as the PI darunavir and least so, the CCR5 co-receptor antagonist maraviroc) when administered at higher than clinical concentrations induced the production of reactive oxygen species in primary cultures of rat astrocytes, suggesting that oxidative stress may represent a mechanism of antiretroviral toxicity. Previous studies comparing clinical symptoms of CNS-toxicity when switching to INSTI-based regimens typically reported beneficial rather than deleterious effects, at least when compared to regimens containing efavirenz, an NNRTI with known risk of inducing neuropsychiatric symptoms. For example, Nguyen et al. (2011) reported better tolerance of raltegravir than efavirenz, although raltegravir was also associated with adverse neuropsychiatric outcomes in 23% of the cohort (efavirenz: 38%). Likewise, Elliot et al. (2019) also found that 6 months following a regimen switch from a non-dolutegravir based ART regimen to a dolutegravir based ART regimen participants showed a significant increased in both executive function and global cognitive function. Keegan et al. (2019) recently observed decreased self-reported CNS toxicity (e.g., depression, insomnia, confusion, impaired concentration, aggression) when switching from efavirenz to dolutegravir. This was associated with increases in plasma concentrations of kynurenine (a metabolite of tryptophan), suggesting changes to serotonergic functioning after initiating dolutegravir treatment. Changes to kynurenine metabolism and their linkage to immune function are well documented in HIV/AIDS (Bipath,

Levay, & Viljoen, 2016; Boasso et al., 2007; Heyes, Rubinow, Lane, & Markey, 1989; Look et al., 2000), as are changes to kynurenine/kynurenine metabolites in neuropsychiatric and neurodegenerative disorders (Erhardt, Schwieler, Imbeault, & Engberg, 2017; Sas, Robotka, Toldi, & Vecsei, 2007). Our findings suggest that INSTI-exposure, and in particular dolutegravir exposure, could exacerbate neurocognitive deficits in PWH perhaps through further dysregulation of kynurenine pathways. Further, indirect effects may include weight, as dolutegravir and other INSTIs have been linked to weight gain (Bourgi et al., 2019; Menard et al., 2017) and weight gain/obesity can exacerbate metabolic, cardiovascular, and other systemic comorbidities implicated in CNS functions in PWH (Feinstein et al., 2019; McCutchan et al., 2012).

Several mental health-related factors were amongst the most important predictors for classification in the neurocognitively impaired group when compared to both the high performing and intermediate group. In the univariate analyses, a significantly higher proportion of individuals in the impaired group was observed to have suicide risk (39.0%), compared to the high performing (13.6%) and intermediate groups (15.8%). In addition, the impaired group reported significantly higher depressive symptomology over the last month. The prevalence of depressive disorders and rates of suicide risk / suicidal behaviour are often elevated among PWH compared to the general population (Hentzien et al., 2018; Jin et al., 2006; Nanni, Caruso, Mitchell, Meggiolaro, & Grassi, 2015; Passos, Souza, & Spessato, 2014). Mental health factors, in particular depression, have well-documented links to neurocognitive impairment in HIV (Carter, Rourke, Murji, Shore, & Rourke, 2003; De Francesco et al., 2019; Rubin & Maki, 2019). Our current findings broadly support these observations. The relatively high importance of suicide risk was unexpected but suggests that in this cohort, suicidality may confer a specific risk

to global neurocognitive impairment. Previous studies outside the HIV literature have suggested suicide attempts to represent a failure of executive control (Bredemeier & Miller, 2015). However, a more comprehensive assessment of past and present suicidal thinking and behaviour, beyond the clinical information available here would be necessary to explore this issue in more detail.

The rates of non-ART medications with possible neurocognitive effects (NC-AEs) also predicted placement in the impaired group, compared to the two better performing groups. Our outcomes support the findings by Rubin et al. (2018), reporting detrimental influences of drugs with anti-cholinergic properties on higher-order cognitive functions (learning/memory; executive functions) in women living with HIV. Drugs with anti-cholinergic properties (see (Radtke et al., 2018) for details) could have interactive and additive effects on neurotoxic viral proteins, exacerbating toxic effects on the brain (Maragos et al., 2003). Polypharmacy is a clinical reality for many PWH and represents an important modifiable risk factor that should be considered in the context of neurocognitive impairment.

A strength of the current study is the use of lifetime-ART duration as a measure of long-term cumulative exposure to ARTs, avoiding some of the ambiguities inherent in the CPE score to approach similar questions. Furthermore, this analytical approach was able to address the inherent confound between age, HIV duration, and ART duration – inevitably, older individuals had a longer disease duration and therefore longer exposure to the ARTs; differences in the timing of market availability of the ARTs would also strongly influence exposure duration. These intrinsic confounds are difficult to disentangle with conventional analytical methods, but adequately addressable with an RFA allowing simultaneous comparison of these variables against each other. Thus, even though age, HIV duration, and treatment duration are necessarily

confounded, our outcomes pointed to a relatively higher importance of the treatment variables (see Figures 5 and 6).

One limitation of this study is its retrospective epidemiological design. While our results pointed to longer ART exposure as an important characteristic of neurocognitive impairment, causality cannot be inferred with this study design. Thus, it remains possible that individuals with lower neurocognitive functions were simply more extensively treated with ARTs – in particular INSTIs. Experimental testing of the mechanistic underpinnings of the relationships between ART exposure, CNS/brain changes, and neuropsychiatric as well as neurocognitive functions in HIV therefore remains crucial. Furthermore, it is also possible that these effects are related to additional treatment factors (e.g., resistance to certain ART) or comorbidities (e.g., HCV-coinfection) which remained unexplored due to the limited number of cases in our cohort of neurocognitively impaired individuals. Finally, because our cohort included only individuals who were born in North America, the current results have limit generalizability and should be explored in larger setting, including higher proportions of female and ethnically diverse participants.

3.5. Conclusion

We found that long-term exposure to ARTs, in particular INSTIs, was a chief characteristic of neurocognitively impaired PWH compared to those without impairment. Although ART are effective and essential for the long-term management of HIV, it remains imperative to understand the adverse potential of longstanding ART treatment. Our findings suggest careful monitoring of neurocognitive functions with longer use of INSTIs.

4. STUDY 2: RELATIONSHIPS BETWEEN MEMORY FUNCTIONS AND ANTIRETROVIRAL MEDICATIONS IN HIV

4.1. Introduction

Neurocognitive impairment as a direct consequence of HIV has long been known. In 1987, Grant et al. published the first comprehensive study of HIV-associated cognitive deficits (Grant et al., 1987). Findings from this study provided evidence that HIV-associated neurocognitive impairments were present throughout every stage of HIV disease and affected multiple cognitive domains including information processing speed, executive functions, and memory. At the time, the (untreated) HIV virus was observed to be distributed preferentially in the basal ganglia, deep white matter and prefrontal cortex (Aylward et al., 1993; Berger & Arendt, 2000; Cornford, Holden, Boyd, Berry, & Vinters, 1992; Navia, Cho, Petito, & Price, 1986; Reyes, Faraldi, Senseng, Flowers, & Fariello, 1991). Thus, in individuals with AIDS, neurocognitive deficits were severe, affected motor and executive functions, and were termed AIDS dementia, a form of subcortical dementia. As a result of these early neuropsychological findings in untreated or mono-therapy-receiving PWH, many studies investigating neurocognitive deficits in HIV have targeted executive and psychomotor functions (functions that heavily rely on the frontostriatal circuitry). Have these typically affected domains changed after the introduction of modern ART? In 2018, Walker and Brown evaluated executive function in HIV in the era of modern ART (Walker & Brown, 2018). Their systematic review compared executive function between PWH and HIV-negative controls across 37 studies conducted from January 2000 to January 2017. Results of this study indicate that across several subtypes of executive functions [according to the framework of Miyake et al. (2000) subdivided into “working memory”, “set shifting”, “inhibition”, and supplemented by studies of “decision making” with tasks like the Iowa

Gambling Task (Bechara, Damasio, Tranel, & Damasio, 2005), PWH performed significantly worse than their HIV-uninfected counterparts. Of the 37 studies included in the review, only one study was longitudinal with the remaining studies following a cross-sectional design. Furthermore, only four of the studies included cohorts in which all patients received ART, resulting in a majority of studies containing a subset of participants who were not treated (percentages of ART-treated ranging from 58% - 100%). Due to the lack of published interventional longitudinal data, the authors extracted the percentage of PWH receiving ART across studies to examine the effects of ART use on executive functions, using a random-effects meta-regression model. Findings indicated that across studies, PWH had lower performance than HIV- controls in all examined executive function domains. However, with increased percentages of ART-treated patients, there was no change in these differences between patients and controls in any of the subtypes of executive function. The authors noted that in several included studies, the HIV cohorts differed substantially from the respective healthy control groups: They were older, less educated, and had higher rates of comorbid substance use, variables known to have a confounding effect on cognitive performance and that could only partly be controlled by normative adjustments. Furthermore, in studies assessing the executive functions "inhibition" and "working memory" there was evidence of publication bias that the authors were unable to account for using statistical corrections. Although these limitations may have hindered the authors' ability to accurately assess the relationship between executive functions and cART or cART status in PWH, their findings do exemplify that executive dysfunctions continue to persist in treated PWH.

The neuropathology of HIV affects brain regions and networks outside of the frontostriatal circuitry (Kato et al., 2020; Sanford et al., 2018), and despite Walker and Brown's

(2018) null findings regarding relationships between executive functions and cART-status, these drugs may still interact with other neurocognitive domains in treated HIV. Among the most pervasively affected neurocognitive domains in PWH are memory functions, estimated to be affected in 40%-60% of PWH (Heaton et al., 2011; Rippeth et al., 2004; Woods et al., 2009).

Memory deficits are one of the strongest neuropsychological predictors of difficulty in conducting activities in daily life and may greatly impact the quality of life of PWH (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009). For instance, the link between poor memory performance and employment status has been established across several studies (Kalechstein, Newton, & van Gorp, 2003; Rabkin, McElhiney, Ferrando, Van Gorp, & Lin, 2004; van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999; van Gorp et al., 2007). Furthermore, deficits in episodic memory tests like the Hopkins Verbal Learning Test – Revised (HVLT-R;(Shapiro, Benedict, Schretlen, & Brandt, 1999) are among the most sensitive indicators of global cognitive impairment in the context of HIV (Carey, Woods, Rippeth, et al., 2004).

Episodic memory, i.e., the ability to learn, store, and retrieve detailed information about unique events, critically relies on the integrity of medial temporal lobe structures including the hippocampus, entorhinal cortex, parahippocampal cortex, and perirhinal cortex (Squire & Zola-Morgan, 1991). Reductions in memory functions in PWH may be due to high levels of HIV virus in the medial temporal lobe regions, inflammation, and downstream structural and functional changes. As such, high HIV viral load was observed in autopsy studies to affect hippocampal regions. For instance, out of seven autopsied brain regions (CA region of the hippocampus, head of the caudate, cerebellar cortex, globus pallidus, mid-frontal cortical gray matter, putamen, substantia nigra) from 12 PWH, Wiley et al. (1998) observed highest HIV RNA in the caudate and the CA regions of the hippocampus. Increased neuroinflammation by microglial activation in

the hippocampus of PWH has also been observed. For example, Anthony, Ramage, Carnie, Simmonds, and Bell (2005) compared microglial inflammation in the hippocampus in 270 PWH to those of healthy controls and found elevated levels of CD68-positive microglia/macrophages in patients. How such changes may interact with ART is not clear. As such, in Anthony et al. (2005), levels of hippocampal neuroinflammation were significantly *higher* in PWH receiving cART (n=42) in comparison to those receiving monotherapy or no treatment (n=228).

Changes within the immune system, such as those in HIV infection, can also facilitate alterations in psychological state including behaviour and mood. Findings from Study 1 indicated that comorbid psychiatric/mood disorders were among the most important predictors of overall neurocognitive status in PWH. It is likely that in HIV, depression and mood changes are at least partly mediated via cytokines, which are known to be linked to psychiatric symptoms irrespective of HIV (Anisman, Merali, Poulter, & Hayley, 2005; Arisi, 2014; Konsman, Parnet, & Dantzer, 2002). For example, pro-inflammatory cytokines such as interleukin-1, interleukin-1β and tumor necrosis factor-α have been associated with sickness behaviour, a set of behavioural changes in mood and anxiety disorders characterized by fatigue, lethargy, excessive sleep and decreased concentration (Anisman et al., 2005; Dantzer, 2001; Rhie, Jung, & Shim, 2020).

Increased viral load as well as microglial activation in HIV infection can both cause an increase of immune response factors such as pro-inflammatory cytokines. Thus, it is possible that both work in a synergistic way to increase neuroinflammation in the medial temporal lobe as well. Irrespective of HIV, increased levels of IL-6, a pro-inflammatory cytokine, have been associated with poorer memory performance in depression (Charlton et al., 2018). Since co-morbid depression is very common in HIV (present in ~40-65% of PWH; (Nanni et al. 2015) and predictive of overall cognitive status in PWH (Gomez, Power, & Fujiwara, 2018), direct and

mood-/depression-related factors in PWH may increase the likelihood of neuroinflammation, perhaps particularly affecting memory-critical areas of the medial temporal lobe (Hein & O'Banion, 2009; Pugh et al., 2000; Richards et al., 2018). How cART may interact with memory functions in PWH has not been explored systematically. The purpose of this review is to determine the effects of cART on memory functions in HIV based on the current literature.

Study goal: Our goal was to examine potential effects of cART on memory performance in PWH, using existing cohort studies. Owing to the conflicting findings on beneficial and – potentially – deleterious effects of cART on cognitive functions (including our own previous findings, chapter 3 (Amusan et al., 2020), we did not formulate directional hypotheses. Several important co-factors we expected may influence memory performance regardless of cART including age, gender, education levels, immune system function (CD4 T-cell count), and comorbid mood disorders.

Working hypothesis: There is a distinguishable role of cART to explain memory performance in treated HIV cohorts, while accommodating other factors known to influence memory.

4.2. Methods

We developed our review protocol according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRIMSA) statement (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

4.2.1. Search Strategy and Data Sources

We conducted a series of searches in EMBASE on June 23rd, 2020 and in CINAHL, MEDLINE and PsycINFO on July 3rd, 2020. We used the search strategy below to retrieve a pool of

potentially relevant articles from the searched databases: Title and abstract search terms included "HIV" (and any of it's iterations) **and** "antiretroviral therapy" (and any of it's iterations, including the names of various ART drug names) **and** terms pertaining to "memory" (including "memory disorder" "neuropsychological tests", "cognitive test", "cognitive measure", "cognitive assessment", "cognitive performance", "cognitive change", "neurocogniti*", "neuropsych*" and names of some specific memory tests like "HVLT", "BVMT"). The search was limited to studies with human participants only. The full search strategy is included in the Appendix (Supplemental Table 4).

4.2.2. Study Selection and Outcome Measures

Two reviewers (the author of the thesis [PA] and co-author Tarek Turk [TT]) independently screened titles and abstracts of the retrieved studies to identify potentially relevant ones. They completed full-text review independently using pre-defined inclusion/exclusion criteria (see below). Disagreements were first resolved between the two reviewers and then by discussion with the team (PA, TT, supervisor Esther Fujiwara [EF]).

4.2.3. Inclusion/exclusion criteria

Studies were considered for inclusion if they evaluated episodic memory in PWH and included information about the patients' cART. Participants must have been over 18 years of age, however there were no limitations on the gender or ethnicity of study participants. Both interventional and observational studies were considered. Longitudinal studies were required to compare participants' memory before and after initiation of cART from being either a) ART-naïve, b) cART-naïve (having only received mono- or dual-therapy), or c) switching from one unsuccessful cART regimen to a new cART regimen. Cross-sectional studies were considered if

they reported the percentage of PWH who were receiving cART at the time of study and a) included at least one control group of PWH who were cART-naïve, or b) included HIV-negative controls. Studies that did not investigate episodic memory or reported episodic memory performance only in a composite measure with other neuropsychological tests (e.g., in form of domain scores) were excluded. Studies that did not include any information about the treatment status of patients (naïve, mono/dual- therapy or cART) or information about the percentage of participants who were receiving cART were excluded. In addition, studies with self-reported memory outcomes (e.g., self-administered surveys) – rather than neuropsychological assessment – and studies that did not explicitly state how memory performance was assessed were excluded.

4.2.4. Data extraction and analysis

Two reviewers (PA and TT) independently extracted the data. The study designs were extracted, with studies falling into one of two main groups: longitudinal studies (i.e., studies that involved following participants with repeated observations of outcomes over an extended period of time) and cross-sectional studies (i.e., studies that examined outcomes at a specified period of time). For longitudinal studies, we distinguished interventional designs (i.e., experimental studies where researchers are providing the intervention such as randomized clinical trials) from observational studies (i.e., studies where researchers are following participants over time to examine associations between different interventions received in the context of their clinical care rather than as part of a study intervention, along with observations of the subsequent outcomes).

Additional extracted data included: length of study and follow-up (longitudinal studies only), publication date and geographical location, as well as demographic information of the cohort [sex (% male), average age (years), average education (years)]. Clinical parameters that

were extracted included: CD4 T-cell count at the study sampling time-points and nadir CD4 T-cell count. Where available, the percentage of participants meeting criteria for a mood disorder was extracted for each study. This percentage was calculated based on any formal mood assessment used in each study (example: CESD (Radloff, 1977), Beck-Depression Inventory-II (Beck, Steer, & Brown, 1996), according to established cut-off scores for these assessment tool. Clinical diagnoses of mood disorders were not pursued due to lack of data. Percentage of participants in each study group receiving cART and type of cART regimen was extracted, and in longitudinal studies along, we also extracted any reported changes to medications (e.g., change from mono/dual- therapy to cART). The names of the neuropsychological memory tests, the outcome measures for each test and the type of reported test score (mean, median, standard deviation or standard error of raw scores, t-scores, and/or z-scores) were also extracted.

Memory findings were extracted and stratified as showing changes (longitudinal studies) or differences to control groups (cross-sectional studies) in the following way: In longitudinal studies, memory was classified as "improved", "unchanged", or "declined" based on the reported changes (p-value <0.05) between baseline and final study time-point, disregarding intermediate time-points (in the case of the clinical trials, this process was done for each clinical arm included in the study). For studies that reported multiple memory scores (i.e., multiple trials of the same test), immediate recall performance (across all trials in list learning tests) and delayed recall performance were inspected for each of the included memory tests per study, i.e., separately for verbal and visual memory tests if present. More peripheral test scores were reported in some studies (e.g., memory intrusions, recognition memory performance, etc.), but not further analysed. If the direction of the inspected memory outcomes agreed (e.g., immediate and delayed recall performance showed improvement in both a verbal and a visual memory test), the study

results were summarized as one memory outcome (in the example, 'improved' memory). If there was disagreement in the direction of the reported memory outcomes within a study, individual results were classified and reported separately (e.g., improvement in immediate and delayed visual memory but no change in immediate or delayed verbal memory). To determine whether there were differences in longitudinal memory changes relative to the cohorts' memory status at the beginning of each study (impaired/unimpaired memory), where reported, standard scores in the memory tests (z-scores; T-scores were converted to z-scale) at baseline and at the final study time-point were calculated, averaging outcomes of immediate and delayed recall performance for each test provided in the studies. An average z-score of less than -1 was used to classify memory status as 'impaired'.

Cross-sectional memory performance in PWH was classified as showing "better", "same", or "worse" performance (p-value <0.05) in comparison to the respective control groups (e.g., mono/dual- therapy treated PWH, ART-naïve and HIV- controls) by first stratifying all reported memory scores into one outcome for each between-group comparison per study. For studies that reported multiple memory scores (i.e., multiple trials of the same test), both immediate recall performance and delayed recall performance were inspected for each test. Similar to the classification procedure for the longitudinal studies, if the direction of the inspected memory outcomes agreed, results were summarized as representing one global memory outcome. If the direction of the inspected outcomes disagreed, results were classified and reported separately. Where available, standard scores (z-scores or T-scores converted to z-scale) were used to assess the presence of memory impairment (reported average z-scores <-1) in PWH to determine whether these cohorts' ART treatment-rates interacted with memory impairment. For studies that reported more than one memory score (i.e., multiple trials of the

same test), both immediate and delayed recall performance were averaged per test. Upon inspection of the available data (only five cross-sectional studies provided standard scores and 2/5 reported averaged standard scores across both visual and verbal memory tests), we decided to further average the outcomes across all tests (regardless of modality) to establish one global memory outcome for each group comparison per study. The presence of memory impairment was also evaluated in studies reporting raw scores converted to z-scores using the reported study controls' means and standard deviations [using the formula: (patient mean raw score – control mean raw score) / control standard deviation]. Upon inspection of the available data, the cross-sectional studies reporting raw scores used a mixture verbal memory and visual tests, with multiple studies reporting a composite score across both types. To maximise the number of studies included in this analysis, all included tests regardless of modality and memory delay were averaged into one global memory outcome per study.

Cohort characteristics years of age, percentage of males, years of education, CD4 cell counts, and percentage of patients with comorbid mood disorder (as available) were compared contrasting longitudinal studies that reported 'improved', 'unchanged', or 'declined' memory performance with t-tests for parametric variables (age, education, CD4 count) or Chi-square tests for frequencies (percentage of males, percentage of patients with mood disorders). For cross-sectional studies, we analysed the percentage of patients on cART, across studies that reported 'better', 'same', or 'worse' memory per each included comparison group. We also compared studies with these different memory results along the same cohort characteristics (age, gender distribution, education, CD4 counts, mood disorders). Each comparison group was inspected separately, i.e., if a cross-sectional study reported worse memory in a HIV+ group compared to an HIV- control group, but equal memory performance in an HIV+ group with comorbid

alcoholism compared to an HIV- group with alcoholism, this study was included twice: In comparisons of cART status and cohort characteristics in studies showing 'worse' memory performance and those showing 'same' performance.

4.2.5. Quality assessment

For assessing the quality of identified studies, two reviewers (TT and PA) working independently conducted an assessment of the level of evidence for each of the included studies using a rating scheme modified from the Oxford Centre of Evidence-based Medicine criteria (Medicine, 2009). Table 4 shows the details of the rating scheme.

Table 4: Quality Rating Scheme (adopted from the Oxford Centre of Evidence-based Medicine)

Rate	Study Design/Evidence Type
1	Properly powered and conducted randomized clinical trial; systematic review with meta-analysis
2	Well-designed controlled trial without randomization; prospective comparative cohort trial
3	Case-control studies; retrospective cohort study
4	Case series with or without intervention; cross-sectional study
5	Opinion of respected authorities; case reports

4.3. Results

After screening 4,080 records, 82 potentially relevant full texts were identified (see Fig. 6). Of these, 44 studies were excluded [31 studies were excluded because they did not include a memory assessment, ten were excluded due to insufficient information on ARTs, and three for missing full texts (e.g., full text not in English, and no full text available). This resulted in 38

studies included for data extraction (Figure 6). After initial data extraction the authors of eleven studies were contacted for additional information including scores on memory tests, and demographic information. Of these, additional information was ultimately obtained for four studies. The remaining seven inquiries either were not responded to, or authors no longer had access to the required information. This resulted in a final total of 31 studies after data extraction, ten longitudinal studies (Table 5, Table 6) and 21 cross-sectional studies (Table 7).

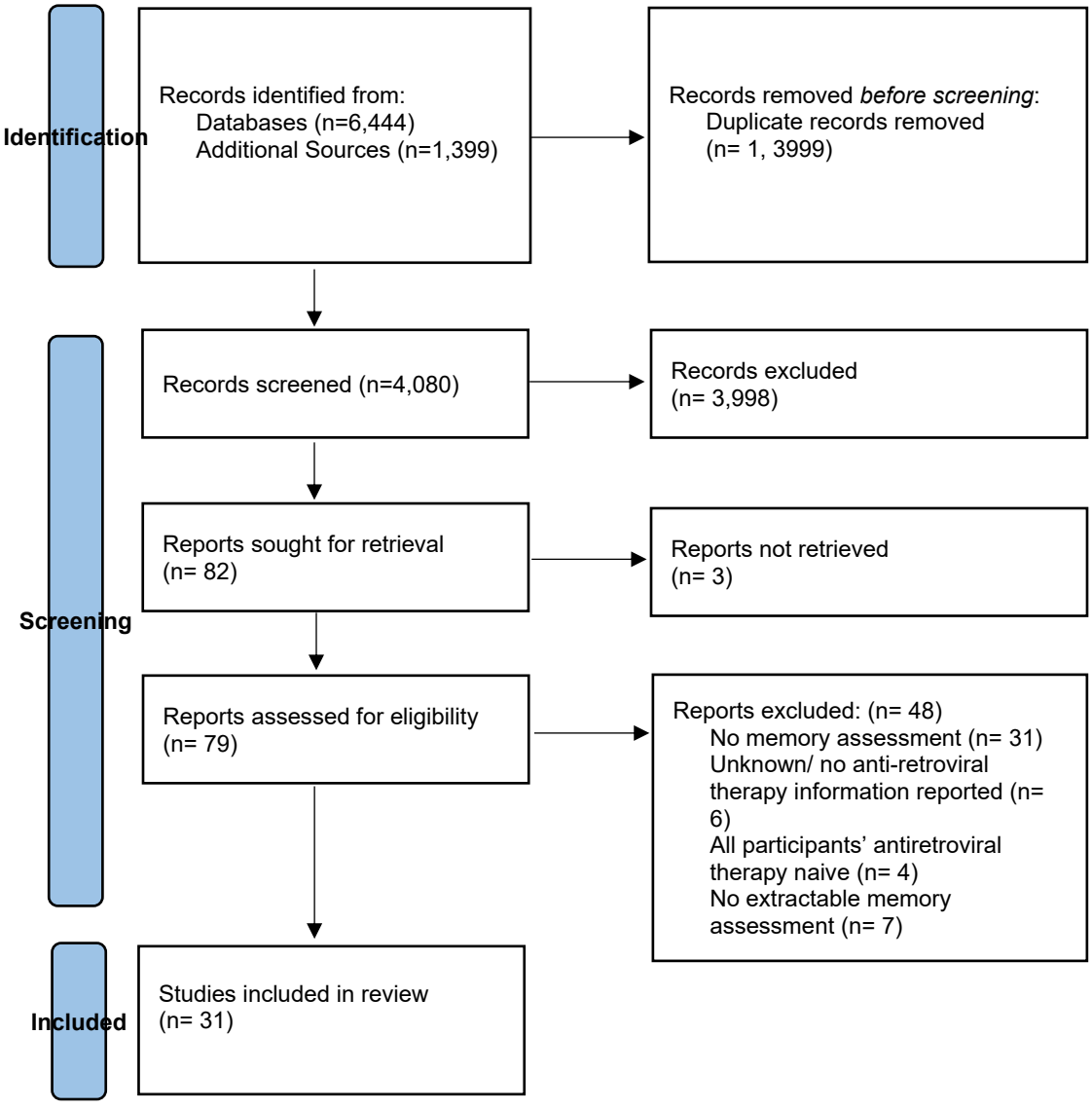


Figure 6. Flowchart diagram of article selection process used for the current analysis. (Page et al., 2021)

4.3.1. Longitudinal studies

The longitudinal studies comprised two clinical trials and eight observational studies (Table 5, Table 6).

Table 5: Longitudinal Studies (Clinical Trials)

Study	Country	Groups & Demographics	ART information	Sampling	Memory Test	Main outcome
Robertson et al. (2016)[-]	USA	G1: N= 119 (88% males), age: 33.0 (24-43) y G2: N=111 (94% males), age: 33.0 (26-42) y	G1: ART Naïve → MVC+DRV+RTV+FTC G2: ART Naïve → TDF+DRV+RTV+FTC	0 – 24 – 48 wk	HVLT	Memory unchanged in both groups
Winston et al. (2016)[-]	Belgium, France, Germany, Ireland, Italy, Spain, UK	G1: N=93 (94% males), age: 36.0 (31-46) y, edu: 13 (10-17) y G2: N=179 (89% males), age: 41.0 (31-48) y, edu: 13 (10-15) y	G1: ART Naïve → DRV+ RTV+RAL G2: ART Naïve → DRV+RTV+TDF/FTC	0 – 96 wk	Free Selective Reminding Test	Memory improved in both groups

[-]:Quality of these studies was rated as 1 (Medicine, 2009): properly powered and conducted randomized clinical trial (see "section 4.2.4" for more details)

Abbreviations; ART: Antiretroviral Therapy, edu: education, DRV: darunavir, FTC: emtricitabine, G1: Group 1, G2: Group 2, HVLT: Hopkins Verbal Learning Test, MVC: maraviroc, RAL: raltegravir, RTV: ritonavir, TDF: tenofovir disoproxil fumarate, TFV: tenofovir

Table 6: Longitudinal Studies (Observational)

Study	Country	Demographics	ART information	Sampling	Memory Test	Main outcome
Ettenhofer et al. (2010)^	USA	N=91 (78% males), age: 42.3±7.7 y, edu: 13.2±2.2 y	cART Naïve/ Unsuccessful cART → novel cART/ new cART regimen	0 – 25 wk	CVLT BVMT	Memory unchanged in CVLT Improvement in BVMT (Immediate and Delayed)
Sacktor et al. (2009)^	Uganda	N=102 (60% males), age: 34.2±6.4 y, edu 9.1±4.3 y	ART Naïve → AZT+3TC+EFV	0 – 12 – 24 wk	WHO/UCLA AVLT	Memory improvement
Carvalhal et al. (2006)^	Brazil	N=14 (57% males), age: 35.5±8.6 y, edu: 8.4±4.0 y	ART Naïve → novel cART	0 – 24 wk	Logical Memory	Memory unchanged
Sacktor et al. (2006)^	Uganda	N=23 (23% males), age: 32.8±1.3 y, edu: 8.7±0.9 y	ART Naïve → d4T+3TC+NVP or ZDV+3TC+TFV	0 – 12 – 24 wk	WHO/UCLA AVLT	Memory improvement
Robertson et al. (2004)^	USA	N=48 (62% males), age: 38.8±7.8 y, edu: 12.5±2.2 y	cART Naïve/ Unsuccessful cART → novel cART/ new cART regimen	0 – 24 wk	RAVLT RCF	Memory improvement
Chang et al. (2003)^	USA	N=33 (86% males), age: 36.5±1.6 y, edu: 12.4±0.5 y	ART Naïve → novel cART	0 – 12 wk	RAVLT	Memory improvement
Tozzi et al. (2001)^	Italy	N=16 (81% males), age: 36.0 (30-57) y, edu: 11.4 (5-17) y	cART Naïve → novel cART	0 – 24 – 60 – 180 wk	RAVLT RCF	Memory unchanged
Tozzi et al. (1999)^	Italy	N=26 (81% males), age: 34.0 (26-57) y, edu: 10.6(8-18) y	cART Naïve → novel cART	0 – 24 – 60 wk	RAVLT RCF	Memory unchanged in RAVLT Memory improved for RCF

^:Quality of these studies was rated as 2 (Medicine, 2009): prospective comparative cohort trial (see "section 4.2.4" for more details)

3TC: lamivudine, ART: Antiretroviral Therapy, AZT: azidothymidine, BVMT: Brief Visual Memory Test, cART: combined ART, CVLT: California Verbal Learning Test, d4T: stavudine, Edu: Education, EFV: efavirenz, NVP: nevirapine, RAVLT: Rey Auditory Verbal Learning Test, RCF: Rey Complex Figure, TFV: tenofovir, WHO/UCLA AVLT: WHO/UCLA Auditory Verbal Learning Test, ZDV: zidovudine

Demographic and clinical details of HIV cohorts from longitudinal studies (N=10): The publication dates spanned from 1999-2016 and studies were conducted in Brazil (N=1), Italy (N=2), the USA (N=4), Uganda (N=2), and in several Western European countries (N=1). The length of the longitudinal follow-up ranged from twelve weeks to 180 weeks. Current CD4 cell count was available for 9 of the studies, with a range of 49.00mm^3/l – 482.87mm^3/l reported. Nadir CD4 cell count was available for only one study (Winston, 2011), reporting 332.00 mm^3/l and 327.00 mm^3/l for the two included HIV+ groups, respectively. Only two of the included studies (Chang et al., 2003; Sacktor et al., 2009) reported information pertaining to mood status in participants, with both studies assessing depressive symptoms in participants using the Center for Epidemiological Studies-Depression (CES-D) with mean scores of CES-D=15.78 and 18.10, respectively (a score of $\geq$ 16 is considered depressed).

Of the ten longitudinal studies, patients either received cART as their first treatment (n=6), after older ART regimens (n=2), or after switching from an unsuccessful to a new cART regimen (n=2; see Figure 7). The majority of the longitudinal study cohorts were predominantly male, with only one of the ten studies reporting a lower percentage of males than females (Sacktor, 2006, 23% males). The mean age of participants in the longitudinal studies ranged from 32.0 – 42.3 years and all studies reporting education data showed that their participants had more than 8 years of education on average (means ranged between 8.4 years – 13.2 years).

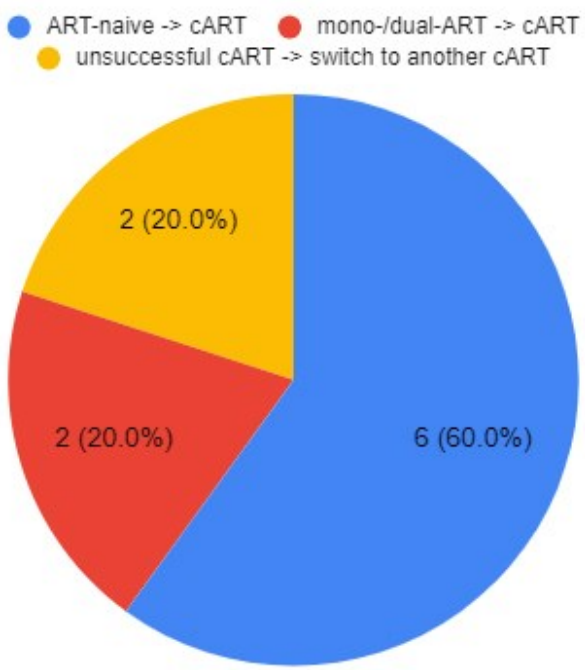


Figure 7. Number of longitudinal studies examining memory functions before and after cART initiation

Memory findings in the longitudinal studies (N=10): As indicated in Table 5 and Table 6 six studies assessed verbal memory only, while four assessed both verbal and visual memory. Tests to assess verbal memory included the HVLT (one study; (Brandt & Benedict, 2001), the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1982; four studies), the Free Selective Reminding Test (Bushke, 1984; one study), the California Verbal Learning Test (CVLT; Delis et al, 1987; one study), the WHO/UCLA Auditory Verbal Learning Test (AVLT; Maj et al. 1993; two studies) and the Logical Memory Test from the WMS (Wechsler, 1987). Visual memory was assessed in four studies in total, with three studies using the Rey Complex Figure Test (RCF; Rey, 1941) and one study using the BVMT (Benedict & Groninger, 1995). In eight studies, global memory outcomes were stratified as 'improved', 'unchanged', or 'decreased', regardless of modality (verbal vs. visual) because they either assessed only one modality or the outcomes

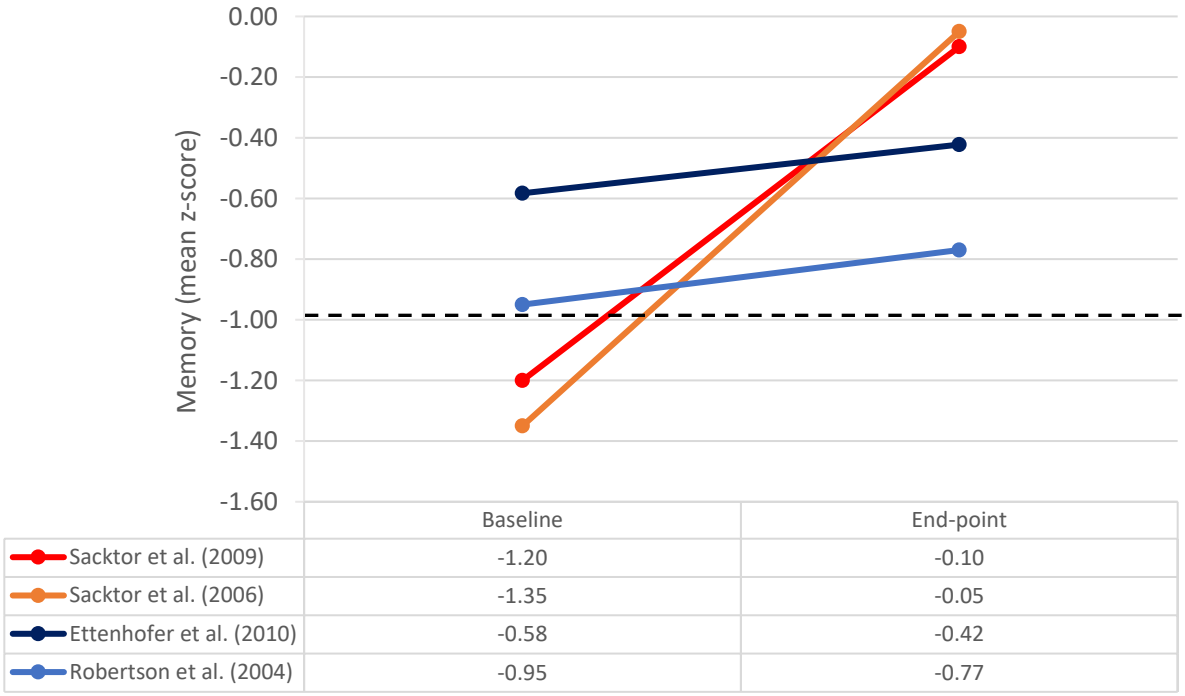
agreed between modalities. Verbal memory outcomes were reported in all ten studies and could therefore be stratified separately. Visual memory outcomes were only available in four studies and not further stratified across studies.

As seen in Table 5, one of the clinical trials (K. R. Robertson et al., 2016) showed unchanged memory performance over a course of 48 weeks while another (Winston et al., 2017) showed improvement over a course of 96 weeks. Among the observational longitudinal studies (Table 6), two studies (Carvalhal, Rourke, Belmonte-Abreu, Correa, & Goldani, 2006; K. R. Robertson et al., 2016; Winston et al., 2017) reported no change in memory performance. Four studies (Chang et al., 2003; K. R. Robertson et al., 2004; Sacktor et al., 2006; Sacktor et al., 2009) reported improvement in memory in either just one measure or consistently in verbal and visual tests; two studies reported improvement (p-value <0.05) in visual memory, but not in verbal memory (Ettenhofer, Foley, Castellon, & Hinkin, 2010; Tozzi et al., 2001). All ten studies used memory tests that assessed both immediate and delayed memory, however only seven studies (Carvalhal et al., 2006; Chang et al., 2003; Ettenhofer et al., 2010; Sacktor et al., 2006; Sacktor et al., 2009; Tozzi et al., 1999; Tozzi et al., 2001) reported scores individually for both immediate and delayed memory. Of these seven studies, outcomes ('improved', 'unchanged', 'declined') were consistent with each other, i.e., no study reported improvement in immediate memory but not delayed memory and vice-versa (not shown in Table 5 and Table 6).

There was no difference in studies that reported memory improvement (N=3) vs. no change in memory (N=5), regarding the respective HIV cohorts' mean age (t[8]=-1.313, p=.313), years of education (t[8]=-0.005, p=.805), CD4 count at baseline (t[8]=.445, p=668) or percentage of males (χ^2[8]=10.00, p=.265). Studies with (n=5) and without (n=5) improved verbal performance also showed no differences in cohorts' mean age (t[10]=-0.500, p=.628), education

(t[10]=.132, p=.898), CD4 count at baseline (χ^2[10]=12.00, p=.285) and gender distribution (t[10]=.471, p=.648). Mood status was only reported in two of the ten studies and not further examined.

Only four longitudinal studies reported memory outcomes as standardized scores relative to population references (Ettenhofer et al., 2010; K. R. Robertson et al., 2004; Sacktor et al., 2006; Sacktor et al., 2009), with all four using verbal memory tests (two studies (Ettenhofer et al., 2010; K. R. Robertson et al., 2004) also assessed visual memory). Therefore, we decided to only inspect any potential differences in trajectories of verbal memory changes. The final sampling time-point was 6-months after baseline in all four of these studies. At baseline, both Sacktor et al. (2006); Sacktor et al. (2009) reported impaired verbal memory performance (z-score <-1), while Ettenhofer et al. (2010) and K. R. Robertson et al. (2004) reported unimpaired verbal memory. After 6 months, all four studies reported unimpaired verbal memory status. Notably, both studies reporting impaired memory performance at baseline included ART- naïve participants, whereas participants in the remaining two studies were not ART-naïve, but initiated cART or switched from an unsuccessful cART regimen (see Figure 8).



	Baseline	End-point
Sacktor et al. (2009)	-1.20	-0.10
Sacktor et al. (2006)	-1.35	-0.05
Ettenhofer et al. (2010)	-0.58	-0.42
Robertson et al. (2004)	-0.95	-0.77

Figure 8. Trajectory of memory changes over time (6-months) in four longitudinal studies as a function of patients' memory status (average z-score relative to normative references) at baseline

4.3.2. Cross-sectional studies

The 21 cross-sectional studies were all observational studies. Of these, seven compared memory performance across more than one population, resulting in 28 distinct comparisons overall. 17 of these studies assessed memory performance in HIV+ cohorts in comparison to HIV-negative controls while three compared memory performance between HIV+ participants on cART and HIV+ participants on non-cART regimens. One study compared performance in ART experienced HIV+ participants and HIV+ participants who were ART-naïve (Table 7).

Table 7: Cross-sectional Studies

Study	Country	Groups & Demographics	ART information	Memory Test	Main Memory Outcome
Spies et al. (2017)*	South Africa	HIV+/Trauma-; N=14, (0% males), age: 35.4±8.0 y, edu: 10.8±1.2 y HIV-/Trauma-; N=32, (0% males), age: 30.4±8.0 y, edu: 11.1±1.3 y HIV+/Trauma+; N=53, (0% males), age: 36.1±6.4 y, edu: 9.8±2.1 y HIV-/Trauma+; N=18, (0% males), age: 30.4±8.0 y, edu: 10.2±3.0 y	HIV+/Trauma-: 68.7% HIV+/ Trauma+: 68.7%	HVLT BVMT	HIV+/Trauma- = HIV-/Trauma- HIV+/Trauma+^{HVLT} = HIV-/Trauma+^{HVLT} HIV+/Trauma+^{BVMT} < HIV-/Trauma+^{BVMT}
Fama et al. (2016)*	USA	HIV+/ALC-; N=36, (64% males), age: 49.5±8.8 y, edu: 13.4±2.8 y HIV-/ALC-; N=31, (53% males), age: 44.1±9.8 y, edu: 15.1±1.9 y HIV+/ALC+; N=42, (62% males), age: 50.1±6.8y, edu: 13.0±2.2 y HIV-/ALC+; N=39, (67% males), age: 48.4±9.7 y, edu: 13.5±2.3 y	HIV+/ALC-:86% HIV+/ALC+:76%	Logical Memory Pattern Recognition Spatial Recognition	HIV+/ALC- < HIV-/ALC- HIV+/ALC+ < HIV-/ALC+
Rubin et al. (2016)*	USA	HIV+/PTSD-; N=830, (0% males), age: 47.3±8.9 y, edu: 12.5±2.9 y HIV-/PTSD-; N=417, (0% males), age: 42.9±10.1 y, edu: 12.6±2.7 y HIV+/PTSD+; N=174, (0% males), age: 48.1±8.0 y, edu: 11.8±3.2 y HIV-/PTSD+; N=79, (0% males), age: 46.7±9.0 y, edu: 11.9±2.9 y	HIV+/PTSD-:77% HIV+/PTSD+:76%	HVLT	HIV+/PTSD- < HIV-/PTSD- HIV+/PTSD+ = HIV-/PTSD+
Kesby et al. (2015)*	USA	HIV+/METH-; N= 31 (100% males), age: 39.2±11.4 y, edu: 14.0±2.0 y HIV-/METH-; N=36 (100% males), age: 34.9±12.4 y, edu: 13.7±2.1 y HIV+/METH+; N=29 (100% males), age: 40.4±8.0 y, edu: 13.3±2.4 y HIV-/METH+; N=25 (100% males), age: 38.4±9.8 y, edu: 12.0±1.7 y	HIV+/METH-:56.7% HIV+/METH+:60.7%	HVLT BVMT	HIV+/METH- = HIV-/METH- HIV+/METH+ = HIV-/METH+
Maki et al. (2015)*	USA	HIV+; N=1,019, (0% males), age: 47.5±8.8 y, edu: 12.4±2.9 y	HIV+:76%	HVLT	HIV+ < HIV-

Study	Country	Groups & Demographics	ART information	Memory Test	Main Memory Outcome
		HIV-; N=502, (0% males), age: 43.5±10.0 y, edu: 12.5±2.8 y			
Tang et al. (2015)*	Canada	HIV+; N=21, (66% males), age: 37.5±9.0 y, edu: 10.3±2.6 y HIV-; N=22, (59% males), age: 39.6±9.0 y, edu: 12.1±1.3 y	HIV+:71%	CVLT	HIV+ < HIV-
Chang et al. (2014)*	USA	HIV+/APOEε4+; N=23, (87% males), age: 47.0±2.9 y, edu: 14.6±0.5 y HIV-/APOEε4+; N=28, (82% males), age: 45.3±2.5 y, edu: 14.8±0.4 y HIV+/APOEε4-; N=57, (93% males), age: 47.4±1.1 y, edu: 15.0±0.3 y HIV-/APOEε4-; N=69, (90% males), age: 44.5±1.5 y, edu: 14.9±0.3 y	HIV+/APOEε4+:93% HIV+/APOEε4-:91%	RAVLT RCF	HIV+/APOEε4+ < HIV-/APOEε4+ HIV+/APOEε4- < HIV-/APOEε4-
Connolly et al. (2014)*	USA	HIV+; N=21, (90.5% males), age: 40.8±2.6 y, edu: 13.8±0.5 y HIV-; N=19, (94.7% males), age: 38.1±2.5 y, edu: 14.4±0.5 y	HIV+:71%	HVLT BVMT	HIV+ = HIV-
Rubin et al. (2014)*	USA	HIV+; N=708 (0% males), age: 44.6±7.4 y, edu: 12.4±2.9 y HIV-; N=278 (0% males), age: 42.8±7.5 y, edu: 12.5±3.0 y	HIV+:66%	HVLT	HIV+ < HIV-
Byrd et al. (2013)*	USA	HIV+; N=30, (50% males), age: 46.4±8.2 y, edu: 11.5±2.5 y HIV-; N=30, (67% males), age: 47.8±8.8 y, edu: 11.5±2.2 y	HIV+:63%	HVLT BVMT	HIV+ = HIV-
Chang et al. (2011)*	USA	HIV+/APOEε4-; N=47, (94% males), age: 47.0±1.2 y, edu: 14.7±0.4 y HIV-/APOEε4-; N=54, (91% males), age: 45.8±1.8 y, edu: 14.7±0.3 y HIV+/APOEε4+; N=22, (86% males), age: 48.3±2.7 y, edu: 14.5±0.5 y HIV-/APOEε4+; N=16, (81% males), age: 46.0±3.2 y, edu: 15.8±0.5 y	HIV+/APOEε4-:79% HIV+/APOEε4+:82%	RAVLT RCF	HIV+/APOEε4- = HIV-/APOEε4- HIV+/APOEε4+ < HIV-/APOEε4+
Fama et al. (2009)*	USA	HIV+/ALC-; N=40, (70% males), age: 41.8±9.7 y, edu: 14.0±2.8 y HIV-/ALC-; N=39, (56% males), age: 40.4±10.1 y, edu:15.0±2.1 y	HIV+/ALC-:63% HIV+/ALC+:47%	The MicroCog – Assessment of Cognitive Functioning	HIV+/ALC- = HIV-/ALC- HIV+/ALC+ = HIV-/ALC+

Study	Country	Groups & Demographics	ART information	Memory Test	Main Memory Outcome
		HIV+/ALC+; N=47, (81% males), age: 44.9±7.0 y, edu: 13.0±2.2 y HIV-/ALC+; N=38, (63% males), age: 42.8±9.4 y, edu: 13.4±1.9 y			
Maki et al. (2009)*	USA	HIV+; N=51, (0% males), age: 43.4±6.8 y, edu: 11.9±2.3 y HIV-; N=12, (0% males), age: 42.9±5.5 y, edu: 12.9±2.2 y	HIV+:61%	HVLT RCF	HIV+ < HIV-
Chang et al. (2008)*	USA	HIV+; N=24, (71% males), age: 44.5±11.9 y, edu: 13.4±1.9 y HIV-; N=14, (71% males), age: 40.8±12 y, edu: 15.0±2.3 y	HIV+:90%	RAVLT	HIV+ = HIV-
Tozzi et al. (2007)*	Italy	HIV+/ART Experienced; N=32, (78.1% males), age: 43.9±6.8 y, edu: 10.9±3.6 y HIV+/ART Naïve; N=62, (83.9% males), age: 40.7±8.8 y, edu: 10.8±4.3 y	HIV+/ART Experienced:34%	RAVLT RCF	HIV+/ART Experienced = HIV+/ART Naïve
Hardy et al. (2006)*	USA	HIV+; N=67, (66% males), age: 47.6±15.5 y, edu: 12.7±2.3 y HIV-; N=19, (66% males), age: 43.8±8.1 y, edu: 13.9±2.1 y	HIV+:100%	CVLT	HIV+ = HIV-
Cysique et al. 2004*	USA	HIV+/cART; N=56 (100% males), age: 48.3±9.4 y, edu: 14.2±2.7 y HIV+/neuro cART; N=41 (98.9% males), age: 48.3±9.6 y, edu: 13.9±3.2 y HIV-; N=30 (100% males), age: 47.4±9.4 y, edu: 15±3.1 y	HIV+:100%	CVLT	HIV+ & HIV+/neuro cART < HIV-
Richardson et al. (2002)*	USA	HIV+/cART; N=82 (0% males), age: 37.0±7.4 y, edu: 11.8±2.3 y HIV+/ART naïve; N=67 (0% males), age: 36.4±7.5 y, edu: 11.3±2.5 y HIV-; N=82 (0% males), age: 34.6±8.8 y, edu: 11.9±1.9 y	HIV+:100%	WHO/UCLA AVLT	HIV+/cART = HIV+/ART naïve = HIV-
Sacktor et al. 2002*	USA	HIV+/cART; N=251 (66.5% males), age: 41.4±7.3 y, edu: 12.3±2.1 y HIV+/noncART; N=272 (77.9% males), age: 39.7±7.5 y, edu: 13.5±2.9 y	HIV+/cART:68% HIV+/nonCART:44%	RAVLT RCF	noncART = cART
Cohen et al. (2001)*	USA	SD cART; N=23 (0% males), age: 33.2±8.4 y, edu: 12.2±2.5 y	SD cART:100% LD cART:100%	Four Word Recall Test	SD cART = LD cART = Non-cART

Study	Country	Groups & Demographics	ART information	Memory Test	Main Memory Outcome
		LD cART; N=32 (0% males), age: 33.2±8.4 y, edu: 12.2±2.5 y Non-cART; N=70 (0%males), age: 33.2±8.4 y, edu: 12.2±2.5 y	Non-cART:100%		
Ferrando et al. (1998)*	USA	HIV+/cART; N=69 (100% males), age: 41.0±7.0 y, edu: 61±88 y HIV+/non-cART; N=69 (100% males), age: 42.0±8.0 y, edu: 52±85 y	HIV+/cART:100% HIV+/non-cART:100%	CVLT	cART > non-cART

*:Quality of these studies was rated as 4 (Medicine, 2009): case series with or without intervention; cross-sectional study (see "section 4.2.4" for more details)

ALC: Alcohol, ART: Antiretroviral Therapy, BVMT: Brief Visual Memory Test, cART: combination ART, CVLT: California Verbal Learning Test, Edu: Education, HVLT: Hopkins Verbal Learning Test, LD: Long Duration, METH: Methamphetamines, RAVLT: Rey Auditory Verbal Learning Test, RCF: Rey Complex Figure, SD: Short Duration, WHO/UCLA AVLT: WHO/UCLA Auditory Verbal Learning Test

Demographic and clinical details of participants in cross-sectional studies (N=21): Studies' publication dates spanned from 1998 to 2017 and the work was conducted in several countries including: Canada (N=1), Italy (N=1), South Africa (N=1), and the USA (N=18). Current CD4 cell count data were available for 18 of the studies, with a range of 76.00mm^3/l – 576.50mm^3/l reported. 17 studies reported information pertaining to mood in participants. Depressive symptoms in participants were assessed using the CES-D (five studies), Beck Depression Inventory (six studies), Hospital Anxiety and Depression Scale (one study), or Hamilton Depression Rating Scale (one study).

Regarding gender distribution, five studies were conducted in female-only cohorts (four in the WIHS cohort), while two studies were conducted with male-only cohorts. Of the remaining 14 studies, the majority of participants were male (between 50% and 94% males). The average age of participants in the cross-sectional studies ranged from 30.37 years to 48.40 years. All studies reported that their participants on average had more than 9 years of educations (reported means between 9.79 and 15.00 years of education). The majority of HIV+ participants (mean: 75.89%) were receiving ART treatment, with ranges between 34.0% and 100% across studies.

Memory findings in the cross-sectional studies (N=21): Eleven studies assessed verbal memory only, while ten assessed both verbal and visual memory, but verbal and visual memory outcomes were reported separately only for 17 studies. Immediate and delayed memory outcomes were reported separately in 12 of the 17 studies that assessed both immediate and delayed memory. Tests to assess verbal memory included the: CVLT (four studies), Four Word Recall Test (Morrow & Ryan, 2002); one study), HVLT (eight studies), Logical Memory (one study), RAVLT (five studies) and WHO/UCLA AVLT (one study). Visual memory was assessed via the

BVMT (four studies), RCF (five studies), Pattern Recognition (Cambridge Neuropsychological Test Automated Battery; Robbins & Sahakian, 1980; one study) and Spatial Recognition from the Cambridge Neuropsychological Test Automated Battery (Robbins & Sahakian, 1980; one study).

In all but one of the 28 comparisons from the 21 cross-sectional studies, group differences in memory performance showed the same direction regardless of modality (i.e., HIV+ cohorts performed either 'worse' or the 'same' in both verbal and visual memory tests as their comparison groups, with the exception of Spies et al. 2017, see below). Thus, cross-sectional study outcomes were stratified as representing global memory, not further evaluating any differential outcomes in verbal, visual, delayed or immediate memory. We first report on studies that compared PWH receiving cART to those receiving non-cART regimens (mono/dual ART). This is followed by studies comparing memory performance in PWH and HIV-negative controls.

HIV+ participants on cART showed better performance than HIV+ participants on non-cART (mono/dual ART) regimens in one study (Ferrando et al., 1998) and better performance than ART-naïve patients in another (Tozzi et al., 2007). The two remaining studies that compared HIV+ individuals receiving cART to those on non-cART regimens showed no memory differences between the two groups (Cohen et al., 2001; Sacktor et al., 2002).

Compared to HIV-negative controls, PWH showed lower memory performance in seven studies (Chang et al., 2014; Cysique et al., 2004; Fama, Sullivan, Sassoon, Pfefferbaum, & Zahr, 2016; Maki et al., 2009; Maki et al., 2015; Rubin et al., 2014; Tang et al., 2015) and similar memory performance in another seven studies (Byrd et al., 2013; Chang et al., 2008; Connolly et al., 2014; Fama, Rosenbloom, Nichols, Pfefferbaum, & Sullivan, 2009; Hardy, Hinkin, Levine,

Castellon, & Lam, 2006; Kesby et al., 2015; Richardson et al., 2002). Three studies examining different comparison groups indicated different memory outcomes depending on the population. Spies, Fennema-Notestine, Cherner, and Seedat (2017) reported worse memory performance in PWH who had experienced trauma in comparison to HIV- controls who had also experienced trauma (defined as: a score of >41 on the Childhood Trauma Questionnaire Short Form; (Bernstein et al., 2003). However, no difference between PWH without trauma and HIV- controls without trauma emerged. Chang et al. (2011) found similar memory performance in PWH and HIV- controls in those who had the APOEε^{4-} allele, but better memory performance in HIV- controls in comparison to PWH without the APOEε^{4+} allele. Rubin et al. (2016) reported better memory in HIV- controls compared to PWH without PTSD, but similar memory performance in individuals with PTSD regardless of HIV status.

Of the 21 studies, 17 assessed both immediate and delayed memory, however only twelve studies (Chang et al., 2008; Cysique et al., 2004; Fama et al., 2009; Ferrando et al., 1998; Maki et al., 2009; Maki et al., 2015; Rubin et al., 2016; Rubin et al., 2014; Sacktor et al., 2002; Spies et al., 2017; Tang et al., 2015; Tozzi et al., 2007) reported individual memory performance scores for both immediate and delayed memory, while three studies (Byrd et al., 2013; Chang et al., 2014; Hardy et al., 2006) assessed only delayed memory and one study (Fama et al., 2016) only assessed immediate memory. Across all twelve studies reporting immediate and delayed memory results separately, outcomes were in agreement.

There was no significant difference in the percentage of participants receiving ART in studies that reported worse performance in HIV+ participants and studies that reported no differences in memory performance in HIV+ participants and controls ($\chi^2[36]=22.49$, $p=.29$). In addition, there was no difference in average education years ($t[24]=-0.25$, $p=.81$), age

(t[20]=1.06, p=.30), or percentage of male participants ($\chi^2(30)=15.79$, p=.98) between studies that reported better memory in HIV- participants than controls, compared to studies that reported no memory differences. CD4 cell counts in studies that reported no difference in memory between HIV+ and HIV- participants were slightly lower (347.701 mm^3/l) than in studies that reported better performance in HIV- (439.535 mm^3/l; t[22]=1.803, p=0.085), but this was not significant.

There was a higher percentage of studies in which participants were depressed on average that reported equal memory performance between PWH and HIV- controls, than in studies that reported worse performance in HIV+ participants ($\chi^2(1) = 5.239$, p=.022). This is also illustrated by the fact that mood assessments on average met the cut-off for depression in 8/11 comparisons (73%) in studies with equal memory performance between groups, versus 3/12 comparisons (25%) in studies showing worse memory in HIV+ than HIV- controls.

Only five studies reported memory performance as standard scores (Byrd et al., 2013; Chang et al., 2011; Chang et al., 2014; Kesby et al., 2015; Tozzi et al., 2007). Both Byrd et al. (2013) and Tozzi et al. (2007) reported memory impairment in PWH with z-scores of -1.97 and -2.05 respectively, while the remaining three studies reported memory performance within the normal range. Due to the small number of studies, average ART-rates were not further statistically compared between studies that reported impaired or unimpaired memory performance in their HIV cohorts. However, the outcomes are illustrated in Figure 9.

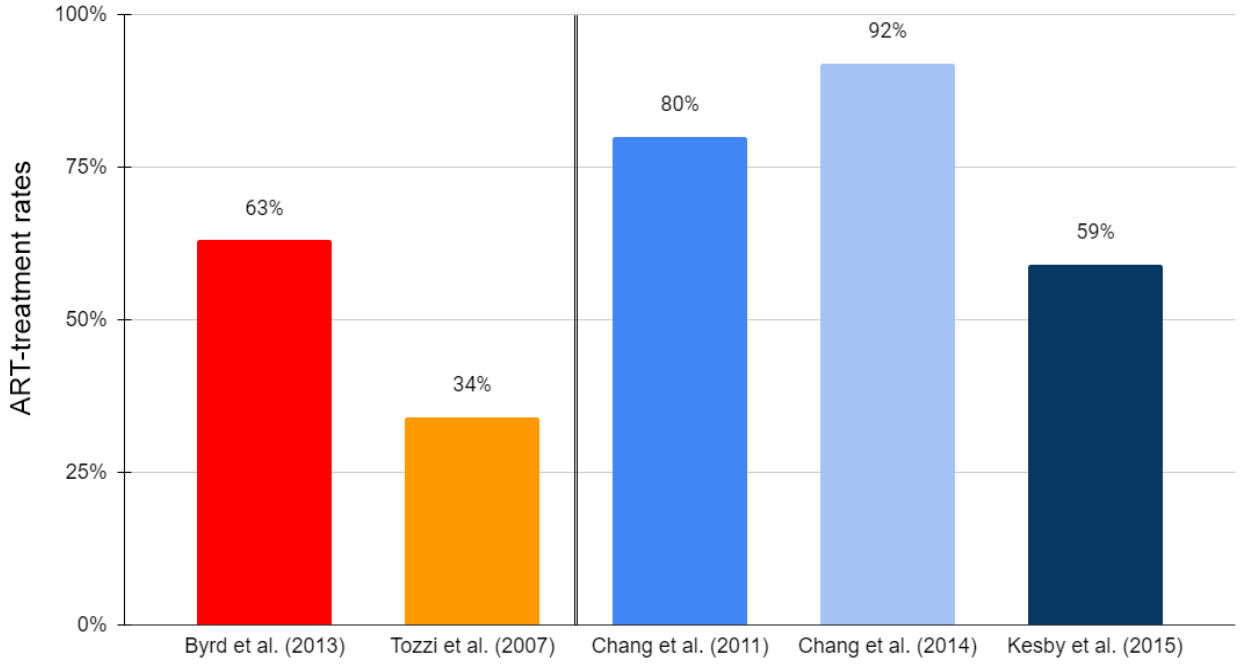


Figure 9. ART-treatment rates in cross-sectional studies reporting impaired (red, orange) or unimpaired (blues) memory status in PWH

In only two (Fama et al., 2016; Tang et al., 2015) of the cross-sectional studies using raw scores memory performance fell inside the impaired range (z-score <-1, relative to study controls), while the remaining 14 reported unimpaired memory. Average ART-treatment rates between these studies was not pursued further due to the scarcity of data.

4.4. Discussion

We conducted a systematic review to determine the potential effects of cART on memory functions in treated HIV. Results on the effect of cART on memory functions were mixed. Among the longitudinal studies after initiation of cART, verbal memory improved over time in 70% (7 out of 10) of the studies. In the cross-sectional studies, memory status in cohorts with variable percentages of cART-treatment rates was mixed, with seven studies indicating equal memory performance in PWH in comparison to HIV- controls, and seven studies reporting worse performance in PWH in comparison to HIV- controls. However, we were not able to observe a pattern of higher or lower cART treatment rates in relation to memory performance in the included cross-sectional studies. Thus, the answer to whether there is a discernable role of cART on memory function remains complicated.

The inability to isolate the role of cART on memory functions in PWH from the literature was due to multiple factors. First, there was a very limited number of interventional studies. Only two of the 31 studies included in this review were randomized controlled trials, with the remaining 29 being observational studies. Therefore, any conclusions about the role of ARTs on memory functions were limited due to the design of the studies included in the review. A lack of interventional studies was also noted by Walker and Brown (2018), a similar systematic review (and meta-analysis), focusing on executive functions in HIV. In their 47 included studies, none were interventional and only one was a longitudinal study. Further complicating factors were the heterogeneity of the memory assessments across the studies as well as the multiple study designs. As such, across the 31 studies, there were a total of 12 distinct memory tests (8 verbal memory tests, 4 visual memory tests), with nine of the 31 studies reporting standardized scores relative to published normative reference data and 22 reporting raw scores. We summarized

memory outcomes as best as possible based on the available data into visual, verbal, immediate, and delayed memory changes (in longitudinal studies) or group differences (in cross-sectional studies). However, this necessarily required (over-)simplification and equating memory performance across different tools and regardless of the comparison group(s). Even just within the longitudinal studies, there were three distinct designs with regard to cART initiation: Cohorts of ART-naïve PWH starting cART, cART-naïve (mono-/dual- therapy receiving) individuals starting cART and individuals switching from an unsuccessful cART regimen to a new cART regimen. Thus, even though our coarse outcomes classification into 'improved' or 'unchanged' memory after cART initiation (or 'same'/ 'worse' memory in cART-treated PWH compared to respective control groups) can be considered appropriate on a descriptive level, meta-analytical quantification of these outcomes would be difficult given the heterogeneity of measures, study designs, and cohorts. Finally, only six of the 31 included studies in fact reported detailed information on cART regimens in the form of listing each drug included in each regimen, whereas the majority of studies instead reported ART information in ways that did not allow the disentanglement of the exact composition of each regimen that was used. For example, some studies reported the number of participants receiving specific ART drugs but no further information on how many drugs each participant was taking or the combinations in which these drugs were taken. Others reported information pertaining to the number of participants receiving regimens that included a specific ART class or the combination of ART classes included in regimens but no information on the specific ART drugs in each regimen. This precluded examining effects of *specific* ARTs on memory function.

Interestingly, major differences between the longitudinal and cross-sectional study cohorts emerged. Keeping in mind that apart from the two RCTs, in both the longitudinal and the

cross-sectional observational studies, the cohorts were likely convenience samples. Descriptively, participants in the longitudinal studies were younger (mean age [range]: 36.1 years [32.8 to 42.3 years]) and had lower CD4 cell counts (mean CD4-counts: 237.8 mm/l) compared to individuals in the cross-sectional studies (mean age [range]: 41.7 years [30.4 to 48.4]; mean CD4-counts: 397.3 mm/l). This could imply that the longitudinal study cohorts may have specifically comprised individuals who were initiating or switching cART regimens to address ill-health while living with untreated or unsuccessfully treated HIV, in contrast to the more varied cross-sectional cohorts. These differences among the populations in the cross-sectional and longitudinal studies further complicate our ability to interpret memory performance as a direct result of ART.

Apart from such limitations in the available literature, several outcomes of this review are of interest. For example, only three (Carvalhal et al., 2006; K. R. Robertson et al., 2016; Tozzi et al., 2001) of the longitudinal studies reported unchanged memory performance from baseline to end of study. In Carvalhal et al. (2006), this result may be in-part due to the inclusion of efavirenz, an NNRTI often linked with neuropsychiatric symptoms and poor cognitive performance (as previously discussed in Section 1.4) in the cART regimen of the participants. Although there was no change in the average memory performance in the entire group of PWH during the study, K. R. Robertson et al. (2016) reported improved memory performance specifically in participants who had been impaired (z-score <-1) at baseline, masked by the non-significant average increase in the entire cohort. Likewise, Tozzi et al. (2001) reported that of the 16 impaired participants at baseline, nine no longer met the requirements for impairment (either performing 1 SD below normative mean on two neuropsychological tests or 2 SD below normative mean in one neuropsychological test) at the conclusion of the study. Furthermore, all

but two participants changed their cART regimen either due to virologic failure, adverse events, or because of the patient's decision. This evidence indicates that although average memory performance remained unchanged in the entire cohorts, cognitive improvements did occur specifically in participants who were globally impaired at baseline, suggesting that the potential for memory improvement after cART initiation/cART switch may depend on impairment status at baseline.

In this regard, four of the longitudinal studies could be well compared (Ettenhofer et al., 2010; K. R. Robertson et al., 2004; Sacktor et al., 2006; Sacktor et al., 2009). These studies were examined to query whether impaired memory at baseline may influence the trajectory of memory changes after cART-initiation. All four studies reported standardized memory scores relative to normative control data, examined verbal memory, and had the same longitudinal follow-up of 6 months (see Figure 9). The two studies reporting impaired memory at baseline (Sacktor et al., 2006; Sacktor et al., 2009)[1] showed improvement after cART initiation, while there were no major changes in memory in the two studies including patients who had unimpaired memory at baseline. Thus, effects of cART on memory may vary as a function of memory impairment at baseline, with a potential recovery of impaired memory but no major changes within the normative range. However, other factors differed between these four studies, including geographical location (Uganda in (Sacktor et al., 2006; Sacktor et al., 2009) vs. USA in (Ettenhofer et al., 2010; K. R. Robertson et al., 2004), limiting the generalizability of these observations. A similar analysis of the cross-sectional studies was limited, as only four (Byrd et

[1] Although these results were seen in two studies from the same research group, there was no overlap of participants across the studies.

al., 2013; Fama et al., 2016; Tang et al., 2015; Tozzi et al., 2007) of the 21 cross-sectional studies included cohorts with (on average) impaired memory. Only five cross-sectional studies reported standardized scores, and of those the two studies including patients with impaired memory relative to controls, had somewhat lower ART-treatment rates (63% and 34%) compared to two of the three cohorts with unimpaired memory (59%-92%; Figure 10).

Seven of the cross-sectional studies investigated other clinical factors and co-morbidities in addition to the role of HIV in memory performance. These included the presence of the APOEε4 allele (Chang et al., 2011; Chang et al., 2014), comorbid alcoholism (Fama et al., 2009; Fama et al., 2016), methamphetamine dependency (Kesby et al., 2015), and trauma experiences or PTSD (Rubin et al., 2016; Spies et al., 2017). Of these seven studies, three reported differences in memory that appeared to be driven by these co-factors rather than by HIV status, whereas four reported similar memory outcomes regardless of these additional factors. Spies et al. (2017) reported better (visual) memory performance in HIV- controls who had experienced trauma (defined as: a score of >41 on the Childhood Trauma Questionnaire Short Form; (Bernstein et al., 2003) in comparison to PWH who had experienced trauma. However, there was no difference between PWH without trauma experiences and HIV-negative controls without trauma experiences. Likewise, results from Chang et al. (2011) indicated better memory performance only in HIV- controls with the APOEε^4 allele in comparison to PWH with the APOEε^4 allele, but no memory differences between PWH without the APOEε^4 allele and controls without APOEε^4 (but see Chang et al., 2014, who reported worse performance in PWH in comparison to HIV- controls regardless of APOEε^4 allele status in a follow-up study in a larger cohort). Both of these results suggest that differences in memory performance between HIV- controls and PWH could be due to non-HIV related factors (i.e., trauma experiences or the

presence of the APOEε^{4+} allele, respectively). Rubin et al. (2016) reported better memory in HIV- controls compared to PWH, but similar memory performance in PWH who had comorbid PTSD compared to HIV- controls with PTSD. This could imply a stronger impact of PTSD (than the presence of HIV) on memory performance in this study.

With regard to comorbid mood disorders/depression, interestingly, in the cross-sectional studies more of the studies with equal memory performance in PWH and HIV- controls contained depressed participants, compared to studies reporting lower memory performance in PWH than controls. This finding was surprising, as memory impairments have previously been associated with depression, anxiety and other mood disorders (Cullen et al., 2019; Hickie et al., 2005; Vance, Larsen, Eagerton, & Wright, 2011) and cognitive impairment is associated with mood disorders such as depression in treated HIV (Rubin & Maki, 2019). However, this finding may have been due to the inclusion of self-report questionnaires to measure depressive symptoms (ie. CES-D, Beck-Depression Inventory, etc.) rather than formal psychiatric diagnosis. More detailed analysis of the role of mood in memory impairments was hindered by the lack of mood assessments, in particular also within the longitudinal studies.

Effects of cART on memory in HIV are difficult to isolate without evidence from randomized controlled trials, and the current systematic review only uncovered two relevant trials in the existing literature. However, a strength of our review is that we were able to include longitudinal evidence at all, albeit mostly of observational nature, and therefore examine reported changes in memory after initiation of cART. Even though the outcomes were mixed, only longitudinal studies can address potential *causal* relationships between cART and memory performance in PWH, and have not been included in previous reviews/meta-analyses on similar topics (executive function, (Walker & Brown, 2018). A major limitation in this literature was the

heterogeneity of memory measures, study designs, as well as demographic/geographical differences between cohorts, limiting our ability to perform a meaningful meta-analysis. Finally, the lack of interventional studies in this field in general limits the interpretation of *specific* ARTs' effects on memory.

4.5. Conclusion

We found there to be mixed evidence on the role of ARTs in memory performance in treated HIV. Given that HIV remains an incurable disease, and that PWH remain dependent on daily ART, it is imperative to understand the role that ART may play as a perpetuating factor in the development of neurocognitive complications and the changing pattern of neurocognitive deficits in PWH.

5. GENERAL DISCUSSION AND CONCLUSION

Treatment strategies for HIV/AIDS have changed dramatically since the start of the epidemic, with modern cART saving millions of lives since their introduction in 1996. If properly treated, PWH are now aging with the disease, with near-identical life expectancies. Despite these tremendous advances in HIV care, there are several complications in the management of HIV that remain. One such complication are cognitive problems in some PWH despite cART. The current thesis specifically sought to address whether the treatment itself might play a role in causing or correlating with cognitive symptoms in PWH. Results of our first study, described in Chapter 3 of this thesis, indicated that lifetime exposure duration to ARTs (in particular the integrase inhibitor dolutegravir), was a unique and important predictor of neurocognitive impairment in PWH, even when controlling for HIV duration, age, and other factors known to be associated with cognition. Results of this study also indicated that among many comorbidities in our cohort, psychiatric/mood symptoms were highly relevant to patients' cognitive status.

These outcomes motivated our second study, described in Chapter 4 of this thesis, a systematic review of current evidence on the role of cART in memory performance in PWH, i.e., a cognitive function, irrespective of HIV status, is related to neuropsychiatric symptoms and integrity of the medial temporal lobe. Results of our second study were mixed. While the majority of longitudinal studies in HIV cohorts initiating cART reported improved memory performance over time, this evidence was based largely on retrospective, observational (i.e., non-interventional) studies. Evidence from cross-sectional studies examining cART treatment rates together with memory performance was inconclusive. Detailed cART information was largely missing in the published studies such that identifying any potential effects of *specific* cART regimens or individual drugs on memory performance was not possible. Together these results

indicate that although ART may play a role in neurocognitive functions in treated HIV, causational evidence remains difficult to extract from patient studies.

Elucidating the specific role of ARTs in cognitive impairment in HIV is a difficult task. The majority of information on neurocognitive performance in PWH in the current literature is observational. Although our first study allowed the statistical separation of ART exposure from other highly correlated factors such as age and HIV duration, the nature of its retrospective epidemiological design does not allow interpretation of a causal relationship between ART and cognition. This limitation is does not affect our study alone, as evidenced by the lack of interventional studies included in the systematic review. While observational studies, like almost all studies included in the review, are able to describe and provide information on the relationship between ARTs and cognitive performance, extracting what specific role ARTs may play amongst the additional comorbidities and other, often inter-correlated factors that may also contribute to cognitive impairment remains beyond their scope. The lack of interventional studies included in previously conducted systematic reviews and meta-analyses investigating similar topics such as Walker and Brown (2018), Gao et al. (2020) and Al-Khindi, Zakzanis, and van Gorp (2011) which included 0/37, 0/16 and 2/24 interventional studies in their reviews, respectively. Similar to our study, these reviews came to descriptive conclusions about trends within the literature, rather than definitive answers on what the role of ARTs may be in cognition in PWH. Although these reviews, along with our own, contribute important descriptive and analytical information they serve as further confirmation that to thoroughly isolate the role of ARTs in neurocognitive performance in PWH, the cause-and-effect relationship between them must be investigated and interventional studies, ideally randomized controlled trials, are imperative to this process.

In addition to human trials, experimental testing of the relationship between ARTs (in general, but also specific drugs and classes) and neurocognitive performance should be systematically pursued. Experiments using direct applications of ARTs on post-mortem human brain tissue or animal tissue at therapeutic doses can provide insight into mechanistic underpinnings of the relationship between ART, neurotoxicity, and neurocognitive functions. It is important to note however, that imperative to these types of studies is an understanding of the therapeutic doses at which ARTs are available within the CNS. Although there are issues with penetrance ranking systems currently in place such as CPE (as discussed in Chapter 1), understanding the ability of ARTs to penetrate the CNS remains crucial in understanding the role ARTs play in perpetuating neurotoxicity. Additional ranking systems, such as the monocyte efficacy score as proposed by Shikuma et al. (2012) may provide alternative measures of successfully classifying ART CNS penetrance. It is important that future CNS effectiveness ranking systems of ART take into account not only the ability of ART drugs to cross the BBB, but also their potential for neurotoxic effects. Additionally, transgenic rodent models may also provide an alternative method of investigating the role of ARTs in cognition as they provide an in vivo model that allows for experimental interventions that are not permissible in clinical studies in PWH (Honeycutt & Garcia, 2018; Marsden, 2020; Vigorito, Connaghan, & Chang, 2015). These animal models also allow for increased control in isolating ART specific brain changes from changes seen as a result of other co-morbid factors. Although HIV is a human-specific pathogen, several animal models have been developed to mimic the HIV-induced neurocognitive deficits seen in PWH. Although the assessment of cognition within animal models is limited, they are still able to provide a more ethical avenue in which cause-effect relationships between ART and neurotoxicity can be investigated. For example, animal models

are better suited to compare an ART regimen or drug to placebo rather than to another ART regimen as is often seen in clinical trials due to the ethics surrounding giving placebos to PWH who are in need of treatment (De Zulueta, 2001; Levine et al., 1999; Mabunda, 2001).

Even though the exact relationships between cART and cognitive functions in PWH may still be unclear, in recent years, questions have been raised about the idea that cART must consist of three or more medications. With improvements in drug development resulting in more tolerable drugs with high potency but decreased potential for triggering the development of ART-resistance, interest has re-emerged for strategies containing fewer ART medications (Soriano et al., 2017). In addition, concerns over access to multiple medications due to factors such as cost, adverse effects caused by drug interactions and decreased drug adherence further motivate the need for simpler regimens (Fernandez-Montero, Eugenia, Barreiro, Labarga, & Soriano, 2013; Llibre & Clotet, 2012), and this development may also simplify our understanding of cause-and-effect in cognitive studies in humans. As least with regard to efficacy, multiple studies have tested dual therapies including two distinct drug classes as initial therapy in ART-naïve PWH and as switch or maintenance therapy in treated PWH who have reached consistent viral suppression (Baril et al., 2016; Soriano et al., 2017). Results remain mixed on whether dual therapy as initial treatment is as efficacious as three-drug regimens. While some results suggest equal levels of viral suppression and occurrence of adverse events in both two-drug and three-drug regimens, other studies show significantly less viral suppression and increased occurrence of adverse events in two-drug regimens (Kozal et al., 2012; Reynes et al., 2011). Likewise, newer studies investigating dual therapy as maintenance therapy options have found that specific combinations such as that of dolutegravir and rilpivirine show promise as non-inferior alternatives to traditional three-drug regimens. However, evidence from two early

failed maintenance trials conducted 20 years ago (Havlir et al., 1998; Pialoux et al., 1998) and newer trials (Bedimo et al., 2014; Pinola et al., 2010) continue to result in reluctance to explore dual regimens as legitimate alternatives. As less complex drug regimens may decrease potential for harmful drug interactions that may lead to neurotoxicity, more evidence is required to properly assess the feasibility of two-drug cART regimens as both initial and maintenance therapy options for PWH.

Finally, considering the very recently proposed framework by Nightingale et al. (2021), our thinking about diagnostic categories of neurocognitive impairment in PWH, as well as formulating potential aetiologies, will likely further evolve. This may result in spectra, types, or patterns rather than distinct classes of cognitive impairment, similar to contemporary approaches to classifying neuropsychiatric disorders (RDoC; (Health, 2009). Considering the multifactorial nature of cognitive problems, specifically in HIV, linking evidence on cART from bench-to-behaviour will remain an important computational challenge in HIV research in the coming years.

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APPENDIX

Table S1. Number of participants taking non-ARV medications with known neurocognitively adverse effects (NC-AE; based on Rubin et al., 2018). Scores are medians (ranges) or patient counts (percent).

	High Performance (n = 132)	**Intermediate Performance (n = 152)**	**Impaired Performance (n = 59)**	**Test Statistic**	**p-value**
All Classes	Med.= 0 (1-5)[a]	Med.= 0 (1-6)[a]	Med.= 0 (0-6)[b]	$\chi^2(2)=24.012$	**<.001**
0	133 (85.6)	116 (76.3)	32 (54.2)		
1	12 (9.1)	21 (13.8)	12 (20.3)		
2+	15 (5.4)	15 (9.8)	15 (25.5)		
Anti-anxiety	Med.= 0 (0-1)[a]	Med.= 0 (0-2)[a]	Med.= 0 (0-2)[b]	$\chi^2(2)=9.465$	**.009**
0	122 (92.4)	141 (92.8)	47 (79.7)		
1	10 (7.6)	10 (6.6)	11 (18.6)		
2+	0	1 (0.7)	1 (1.7)		
Anti-depressant	Med.= 0 (0-2)[a]	Med.= 0 (0-3)[a,b]	Med.= 0 (0-2)[b]	$\chi^2(2)=9.120$	**.010**
0	123 (93.2)	134 (88.2)	46 (78.0)		
1	8 (6.1)	14 (9.2)	11 (18.6)		
2+	1 (0.8)	4 (2.7)	2 (3.4)		
Betablockers	Med.= 0	Med.= 0 (0-1)	Med.= 0 (0-1)	$\chi^2(2)=5.536$	.063
0	132 (100)	151 (99.3)	57 (96.6)		
1	0	1 (0.7)	2 (3.4)		
2+	0	0	0		
Opioids	Med.= 0 (0-1)[a]	Med.= 0 (0-1)[a]	Med.= 0 (0-2)[b]	$\chi^2(2)=7.393$	**.025**
0	131 (99.2)	146 (96.1)	54 (91.5)		
1	1 (0.8)	6 (3.9)	4 (6.8)		
2+	0	0	1		
Muscle Relaxants	Med.= 0 (0-1)	Med.= 0 (0-1)	Med.= 0 (0-2)	$\chi^2(2)=3.273$	.195
0	131 (99.2)	146 (96.1)	58 (98.3)		
1	1 (0.8)	6 (3.9)	1 (1.7)		
2+	0	0	0		

	High Performance (n = 132)	Intermediate Performance (n = 152)	Impaired Performance (n = 59)	Test Statistic	p-value
Antipsychotics	Med.= 0 (0-1)[a]	Med.= 0 (0-1)[a]	Med.= 0 (0-3)[b]	$\chi^2(2)=9.807$	**.007**
0	129 (97.7)	147 (96.7)	52 (88.1)		
1	3 (2.3)	5 (3.3)	6 (10.2)		
2+	0	0	1 (1.7)		
Anti-convulsants	Med.= 0 (0-1)[a]	Med.= 0 (0-1)[a]	Med.= 0 (0-1)[b]	$\chi^2(2)=8.240$	**.016**
0	130 (98.5)	151 (99.3)	55 (93.2)		
1	2 (1.5)	1 (0.7)	4 (6.8)		
2+	0	0	0		
Drugs with anticholinergic properties	Med.= 0 (0-3)[a]	Med.= 0 (0-4)[b]	Med.= 0 (0-4)[b]	$\chi^2(2)=17.605$	**<.001**
0	123 (93.2)	120 (78.9)	42 (71.2)		
1	6 (4.5)	22 (14.5)	9 (15.3)		
2+	3 (2.3)	10 (6.6)	8 (3.4)		
Gastrointestinal agents	Med.= 0 (0-1)[a]	Med.= 0 (0-1)[a,b]	Med.= 0 (0-2)[b]	$\chi^2(2)=7.391$	**.025**
0	131 (99.2)	143 (94.1)	54 (91.5)		
1	1 (0.8)	9 (5.9)	4 (6.8)		
2+	0	0	1 (1.7)		

Med.= Median

Table S2: Overview of demographic variables of all available participants, prior to selecting N=343 who were born in North America; data are number of patients (percentages) or means (standard deviations)

Variable	**All Participants* (N=457)**
Sex (% Male)	394 (86.2%)
Continent of Birth	
North America	343 (75.1%)
South America	19 (4.2%)
Asia	27 (5.9%)
Africa	47 (10.3%)
Europe	19 (4.2%)
Oceania	1 (0.2%)
Age (years)	47.8 (11.0)
Education (years)	13.97 (2.49)

Table S3: Normative references used for each test included in the neuropsychological battery

Test	Adjustment			Reference
	Age	*Education*	*Gender*	
TMT-2	√	√		Fine et al. (2011)
SDMT	√	√		(Smith, 1973)
TMT-4	√	√		Fine et al. (2011)
WCST	√	√		(Kongs et al., 2000)
FAS	√	√		Mitrushina et al. (2005)
Animals	√	√	√	CNNS™, Schretlen et al. (2010)
HVLTimm	√	√	√	CNNS™, Schretlen et al. (2010)
HVLTdel	√	√	√	CNNS™, Schretlen et al. (2010)
GPBdom	√	√	√	CNNS™, Schretlen et al. (2010)
GPBnondom	√	√	√	CNNS™, Schretlen et al. (2010)

Abbreviations. Animals: Delis-Kaplan Executive Function System Category Fluency (animals), FAS: Delis-Kaplan Executive Function System Letter Fluency, GPBdom.: Grooved Pegboard (dominant hand), GPBnondom.: Grooved Pegboard (non-dominant)., HVLT del.: Hopkins Verbal Learning Test (delayed), HVLT imm.: Hopkins Verbal Learning Test (immediate), SDMT: Symbol Digit Modalities Test, TMT-2: Trail Making Test 2, TMT-4: Trial Making Test 4, WCST: Wisconsin Card Sorting Test 64-Card version

Table S4. List of search strategy terms. Each Line represents one element or a collection of elements

1.	exp HIV/
2.	hiv infections/ or acquired immunodeficiency syndrome/ or aids dementia complex/ or hiv seropositivity/
3.	(hiv or human immunodeficiency virus* or "hiv/aids" or acquired immunodeficiency syndrome).mp.
4.	1 or 2 or 3
5.	Antiretroviral Therapy, Highly Active/
6.	exp anti-hiv agents/ or cobicistat/ or delavirdine/ or didanosine/ or efavirenz, emtricitabine, tenofovir disoproxil fumarate drug combination/ or elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate drug combination/ or emtricitabine/ or emtricitabine, rilpivirine, tenofovir drug combination/ or emtricitabine, tenofovir disoproxil fumarate drug combination/ or lamivudine/ or nevirapine/ or raltegravir potassium/ or rilpivirine/ or stavudine/ or tenofovir/ or trichosanthin/ or zalcitabine/ or zidovudine/ or maraviroc/ or enfuvirtide/ or atazanavir sulfate/ or darunavir/ or indinavir/ or lopinavir/ or nelfinavir/ or ritonavir/ or saquinavir/ or reverse transcriptase inhibitors/ or dideoxynucleosides/ or foscarnet/ or phosphonoacetic acid/
7.	(antiretroviral or dolutegravir or elvitegravir or raltegravir or efavirenz or integrase inhibitor* or protease inhibitor* or fusion inhibitor* or non nucleoside reverse transcriptase inhibitor* or nonnucleoside reverse transcriptase inhibitor* or fusion inhibitor* or CCR5 antagonist).mp.
8.	(3TC or ABA or AMP or ATA or AZT or "c/DRV" or D4T or DDC or DDI or DDI-EC or DELOR DRV or DTG or EFA or "ETG/C" or ETR or FOSAPV or FTC or HU or IND or KAL-LQ or KAL-SG or KAL-TB or LOV or MRV or NEV or NFV or RIT or RPV or RTG or SQV-HG or SQV-SG or SQV-TB or T20 or TAF or TEN or TPV or anti-hiv agents or cobicistat or delavirdine or didanosine or efavirenz or emtricitabine or tenofovir or disoproxil fumarate drug combination or elvitegravir or cobicistat or emtricitabine or tenofovir disoproxil fumarate drug combination or emtricitabine or emtricitabine or rilpivirine or tenofovir drug combination or emtricitabine or tenofovir disoproxil fumarate drug combination or lamivudine or nevirapine or raltegravir potassium or rilpivirine or stavudine or tenofovir or trichosanthin or zalcitabine or zidovudine or maraviroc or enfuvirtide or atazanavir sulfate or darunavir or indinavir or lopinavir or nelfinavir or ritonavir or saquinavir or reverse transcriptase inhibitors or dideoxynucleosides or foscarnet or phosphonoacetic acid).mp.
9.	5 or 6 or 7 or 8
10.	Memory Disorders/

11. Memory.mp.

12. exp Neuropsychological tests/

13. (hopkin* verbal learning test or hvlt or bvmt or neuropsych* or cognitive test* or cognitive measure* or cognitive assessment* or cognitive performance or cognitive change or neurocogniti*).mp.

14. 10 or 11 or 12 or 13

15. exp anxiety disorders/ or exp mood disorders/ or exp "trauma and stressor related disorders"/

16. (Depression or depressive or anxiety or stress or post-traumatic stress or PTSD or mood or PHQ-9 or trauma* or mental health or suicid*).mp.

17. 15 or 16

18. Cognition disorders/ or cognitive dysfunction/ or dementia/ or aids dementia complex/ or exp dementia, vascular/

19. ((cognitive adj3 (disab* or impair* or delay* or disorder* or deficit* or dysfunction*)) or brain impairment* or brain damage or dementia).mp.

20. 18 or 19

21. 17 and 20

22. (4 and 9 and (14 or 21)) not ((vaccin* or t-cell*).mp. or encephalitis.ti.)

23. limit 22 to animals

24. limit 23 to humans

25. 22 not (23 not 24)

26. 25 not (rat or rats or mouse or mice or murine or animal model* or monkey or macaque*).ti.

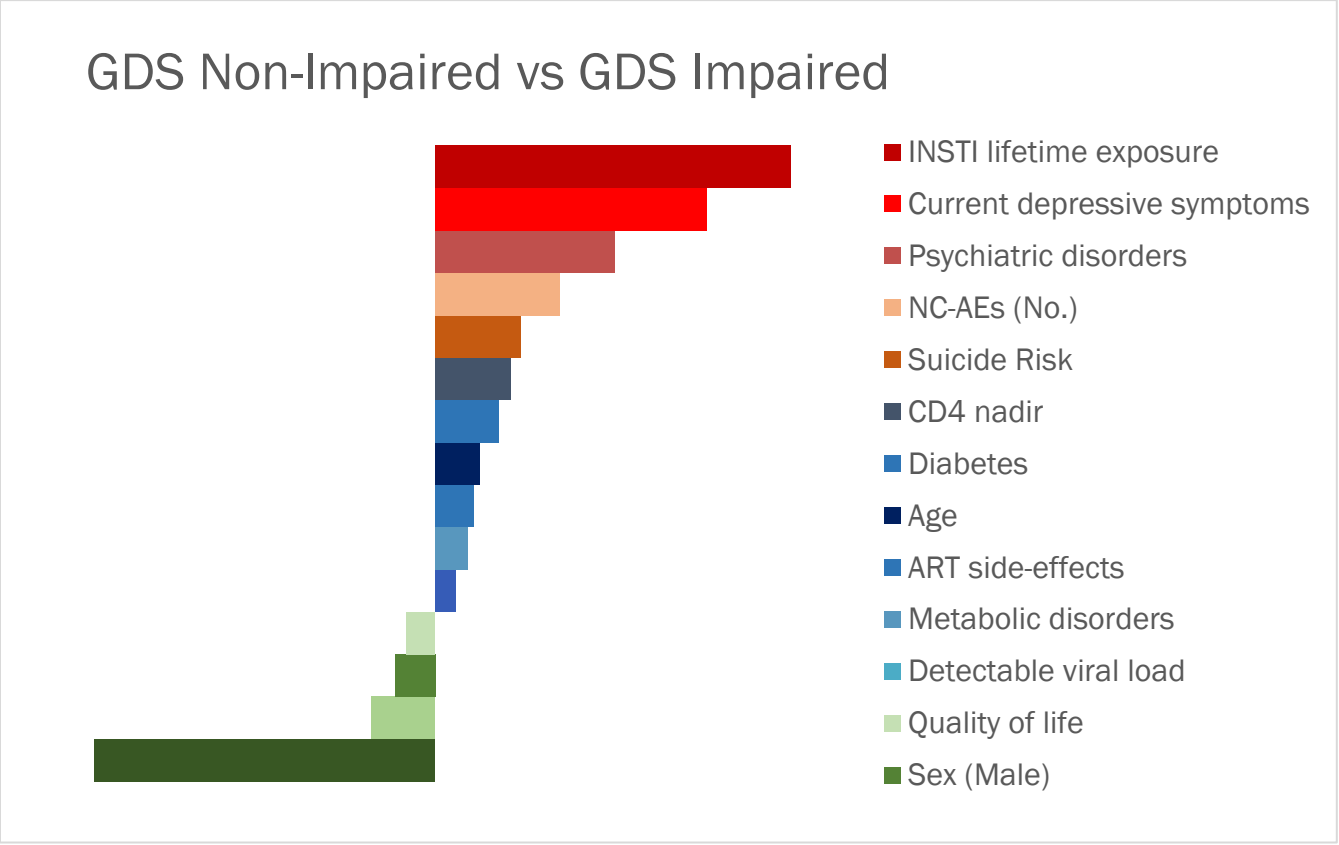

Figure S1. Random Forest Analysis results using a Global Deficit Score (GDS) of 0.5 or higher to define neurocognitive impairment (N=95), compared to a non-impaired group (N=248). Direction of the bars corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis. AUC: 0.83, F_1 score: 0.696.

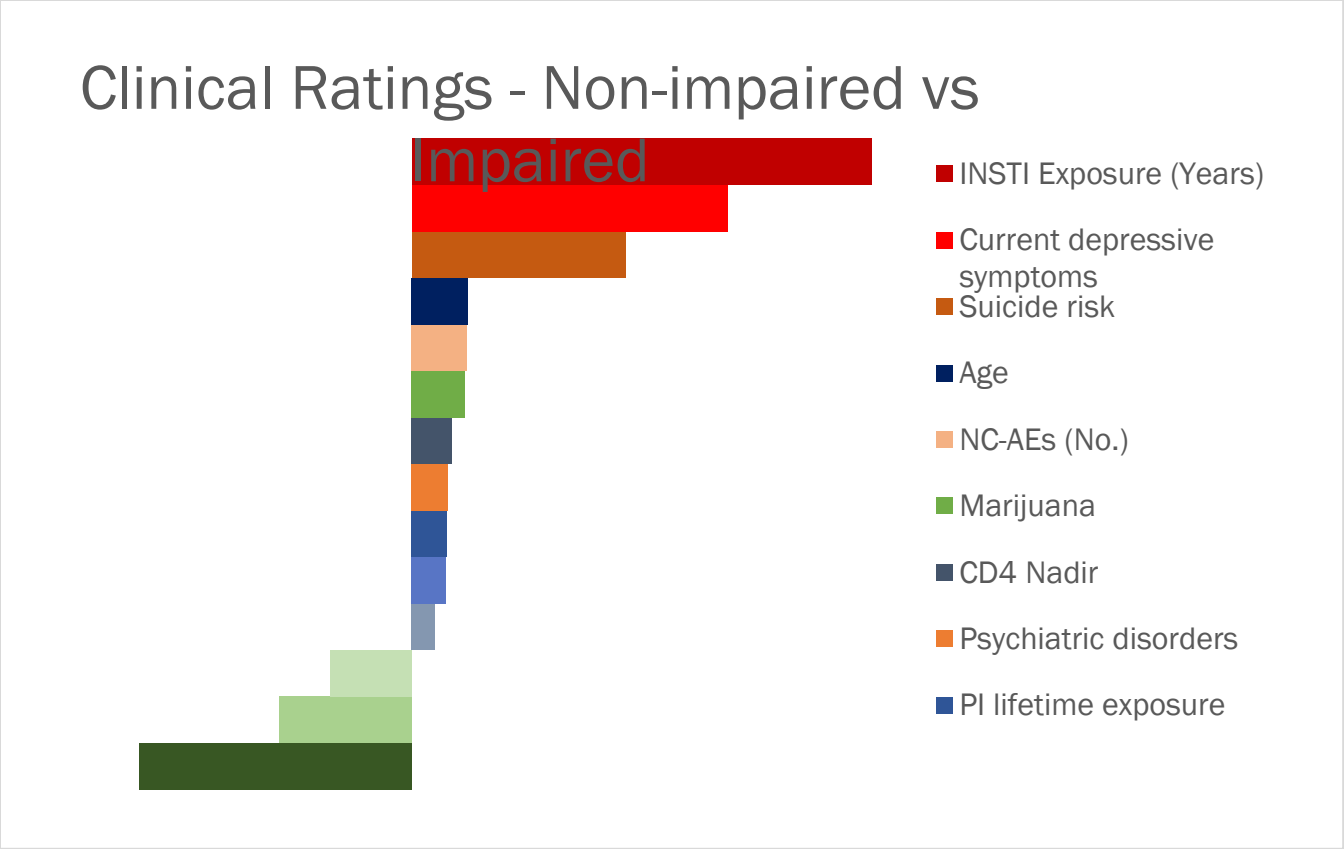

Figure S2. Random Forest Analysis results using impaired Clinical Ratings in two or more neuropsychological domains to define neurocognitive impairment (N=83), compared to a non-impaired group (N=260). Direction of the bars corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis. AUC: 0.84, F_1 score: 0.744.

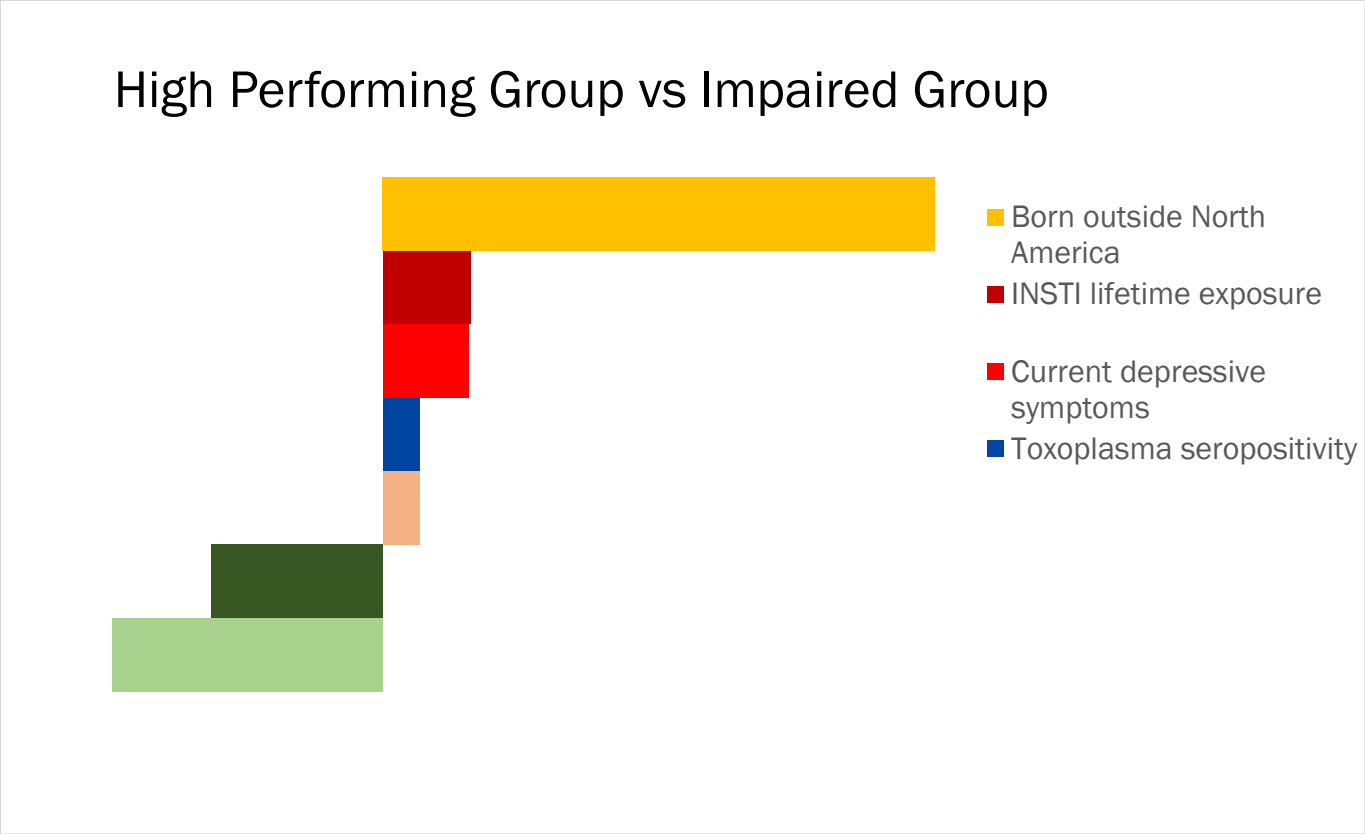

Figure S3. Random Forest Analysis results in all participants (including those born outside North America). High Performing (N=153), Impaired Group (N=111). Direction of the bars corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis. AUC: 0.83, F1 score: 0.89

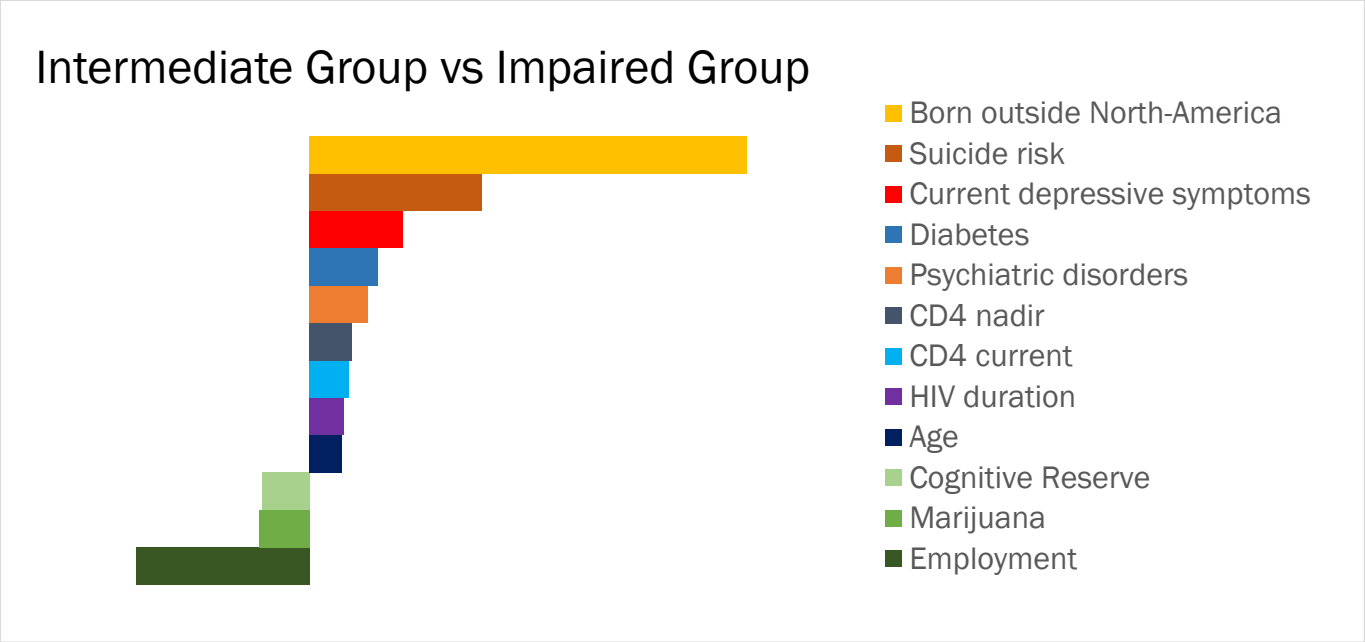

Figure S4. Random Forest Analysis results in all participants (including those born outside North America). Intermediate (N=193), Impaired Group (N=111). Direction of the bars corresponds placement into each group. The magnitude of bars corresponds to the variable importance values in the analysis. AUC:0.78, F1 score: 0.63 (note: this model fit poorly).

Figure S5. Distribution of 59 patients from the neurocognitively impaired profile (ascertained through Latent Profile Analysis) into neurocognitively impaired groups using Global Deficit Scores or Clinical Ratings.