The role of cognitive reserve in protecting cognitive ability in people with HIV

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Abstract

The landscape of HIV-1 disease has radically improved with the contemporary anti-retroviral therapy. However, HIV-associated neurocognitive disorders (HAND) continue to be a challenge even among those with an optimal drug regime. Although neurocognitive deficits are typically of mild nature, the burden associated with HAND is an emerging public health concern due to unrelenting repercussions on everyday functioning including medication adherence, employment, and overall survival. Could people with HIV somehow protect themselves from cognitive impairment? Cognitive reserve is a theoretical entity which has been put forward to offset the deleterious impact of brain pathology on cognitive performance. Although a promising entity, a uniform method to capture cognitive reserve does not exist. This thesis investigated the impact of cognitive reserve on cognitive performance in individuals with HIV.

The thesis commenced with a systematic review and a meta-analysis of the published literature (N=10) to estimate the strength of association between cognitive reserve and cognitive performance in HIV (Manuscript I). The association between the two constructs was found to be moderately strong. This work showed that discrepant indicators have been employed to operationalize cognitive reserve in HIV – with most studies focusing on varying combinations of educational attainment, occupational complexity and IQ. It was found that participation in leisure and social activities was infrequently employed as an indicator of cognitive reserve in these HIV studies. This review produced a framework which hypothesized the mediating role of cognitive reserve on brain pathology and its consequences from the context of rehabilitation.

The second manuscript quantified cognitive reserve into a single numeric value utilizing various indicators which have been proposed to build cognitive reserve. Pertinent data (including education, occupation, social network, number of spoken languages, and participation in other

cognitively stimulating activities) were acquired from a Canadian longitudinal study (N=856) with HIV+ individuals to devise an index of cognitive reserve based on the differential impact of each indicator. This work involved a standard methodology where the regression coefficients for each contributing indicator were used in the scoring algorithm. A correlation coefficient of 0.3 between the developed index and a measure of cognitive performance at follow-up was expected given its hypothesized role as a mediator of cognitive performance rather than having a direct effect.

Engagement in physical activity has been also viewed as a contributor to cognitive reserve through various mechanisms. Manuscript III documented the feasibility and efficacy potential of a 12-week combined aerobic and resistance training program in improving cognitive performance in HIV (N=27). This study was a subset of a cohort multiple randomized controlled trial which provided access to the participants who were eligible for the exercise program. As expected, physical performance measures showed improvements post-training. Good adherence and acceptability of the exercise program was tainted with slow and painstaking recruitment. No positive influence was observed on the primary efficacy potential outcome of cognitive performance.

Lastly, a systematic review was carried out to address some questions which surfaced at the outset of the aforementioned feasibility study. For instance, are pilot and feasibility studies the same? What should be the key objectives of a pilot study? What happens to a pilot study once it is completed? Does an effect size observed in a pilot study predict its follow-up? These questions were addressed based on 191 feasibility studies published in a specific rehabilitation journal since its inception. This work demonstrated that feasibility outcomes were often disregarded in the measurement strategy of these studies. Only a minor proportion of the studies got followed-up in a full-strength clinical trial and effect size did not drive this follow-up. This manuscript

generated key areas of focus relevant to feasibility studies designed in rehabilitation research.

In nutshell, the first three manuscripts contributed evidence towards the impact of cognitive reserve in protecting cognitive performance in people with HIV. The fourth manuscript assisted in better selection of the outcomes in the feasibility study covered in this thesis. It addressed the frequently neglected question whether a feasibility study should be pursued further. Additionally, it is hoped it will serve as a useful primer on the feasibility studies in the field of rehabilitation.

Résumé

Le paysage de la maladie du VIH-1 s'est radicalement amélioré avec les thérapiesantirétrovirales contemporaines. Cependant, les troubles neurocognitifs associés au VIH (HAND) continuent de poser problème, même parmi ceux qui suivent un régime de traitement optimal. Bien que les déficits neurocognitifs soient généralement légers, le fardeau associé au HAND est une préoccupation émergente pour la santé publique en raison des répercussions persistantes sur le fonctionnement quotidien, notamment l'adhérence au médicament, l'emploi et la survie globale. Les personnes vivant avec le VIH pourraient-elles se protéger d'une manière ou d'une autre contre les troubles cognitifs? La réserve cognitive est une entité théorique qui a été mise en avant pour compenser l'impact néfaste de la pathologie cérébrale sur les performances cognitives. Bien qu'il s'agisse d'une entité prometteuse, il n'existe pas de méthode uniforme pour capturer les réserves cognitives. Cette thèse portait sur l'impact des réserves cognitives sur les performances cognitives chez les personnes vivant avec le VIH.

La thèse a débuté par une revue systématique et une méta-analyse de la littérature publiée (N=10) pour estimer la force de l'association entre réserve cognitive et performance cognitive chez les personnes atteintes du VIH (Manuscrit I). L'association entre les deux concepts s'est avérée modérément forte. Ces travaux ont montré que des indicateurs divergents ont été utilisés pour opérationnaliser la réserve cognitive liée au VIH – la plupart des études se concentrant sur différentes combinaisons de niveau d'instruction, de complexité professionnelle et de QI. Il a été constaté que la participation aux loisirs et aux activités sociales était rarement utilisée comme indicateur de réserve cognitive dans ces études sur le VIH. Cette revue a produit un cadre qui a émis l'hypothèse du rôle médiateur des réserves cognitives sur la pathologie cérébrale et de ses conséquences dans le contexte de la réadaptation.

Le deuxième manuscrit a quantifié la réserve cognitive en une valeur numérique unique en utilisant divers indicateurs proposés pour créer une réserve cognitive. Des données pertinentes (comprenant l'éducation, la profession, le réseau social, le nombre de langues parlées et la participation à d'autres activités stimulantes sur le plan cognitif) ont été obtenues à partir d'une étude longitudinale canadienne (N = 856) auprès de personnes séropositives afin de concevoir un indice de réserve cognitive basé sur l'impact différentiel de chaque indicateur. Ce travail a impliqué une méthodologie standard dans laquelle les coefficients de régression pour chaque indicateur de contribution ont été utilisés dans l'algorithme de notation. Un coefficient de corrélation de 0,3 entre l'indice développé et une mesure de la performance cognitive au suivi était attendu compte tenu de son rôle hypothétique de médiateur de la performance cognitive plutôt que d'avoir un effet direct.

L'engagement dans l'activité physique a également été considéré comme un contributeur à la réserve cognitive par le biais de divers mécanismes. Le manuscrit III a documenté la faisabilité et le potentiel d'efficacité d'un programme combiné de 12 semaines d'aérobie et de musculation visant à améliorer les performances cognitives des personnes vivant avec le VIH (N = 27). Cette étude était un sous-ensemble d'essais contrôlés randomisés multiples d'une cohorte qui permettait l'accès aux participants éligibles pour le programme d'exercices. Comme prévu, les mesures de performance physique ont montré des améliorations après l'entraînement. La bonne adhésion et l'acceptabilité du programme d'exercices étaient entachées d'un recrutement lent et laborieux. Aucune influence positive n'a été observée sur le principal critère d'efficacité de la performance cognitive.

Enfin, une revue systématique a été réalisée pour répondre à certaines questions apparues au

début de l'étude de faisabilité susmentionnée. Par exemple, les études pilotes et les études de faisabilité sont-elles identiques? Quels devraient être les objectifs principaux d'une étude pilote? Qu'advient-il d'une étude pilote une fois qu'elle est terminée? Est-ce que l'ampleur de l'effet observé dans une étude pilote prévoit sa suite? Ces questions ont été traitées sur la base de 191 études de faisabilité publiées depuis sa création dans un journal spécifiquement de réadaptation. Ce travail a démontré que les résultats de faisabilité étaient souvent négligés dans la stratégie de mesure de ces études. Seule une petite proportion des études a fait l'objet d'un suivi dans le cadre d'un essai clinique complet et l'ampleur de l'effet n'a pas motivé ce suivi. Ce manuscrit a généré des domaines d'intervention clés pertinents pour les études de faisabilité conçues dans le cadre de la recherche en réadaptation.

En résumé, les trois premiers manuscrits ont apporté des preuves de l'impact de la réserve cognitive sur la protection des performances cognitives chez les personnes vivant avec le VIH. Le quatrième manuscrit a contribué à une meilleure sélection des résultats de l'étude de faisabilité couverte par cette thèse. Il a soulevé la question souvent négligée de savoir si une étude de faisabilité devrait être poursuivie plus loin. De plus, on espère que cela servira d'introduction utile aux études de faisabilité dans le domaine de la réadaptation.

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Preface

Statement of Originality

This thesis constitutes original work which answered questions that were not previously addressed within the neuroHIV literature. The novel contributions of the thesis include: (i) quantification of the association between cognitive reserve and cognitive performance in HIV in the form of a meta-analysis; (ii) construction and validation of a cognitive reserve index in HIV; (iii) evaluating the feasibility and potential impact of a 12-week exercise intervention on cognitive performance using a performance-based measure and (iv) producing recommendations for pilot and feasibility trials in the field of rehabilitation based on previous 30 years of published literature in a specific rehabilitation journal.

Various methods of converting effect sizes were integrated to conduct a meta-analysis which led to the estimation of the relationship between cognitive reserve and cognitive performance in HIV. This work was unique from the perspective that meta-analyses are often abandoned when confronted with diverse effect sizes and/or lack of effect parameters which can be harmonized to compute a summary effect size. The statistical models for each study were written out to have a clear understanding of the relationships under scrutiny – this is an uncommon way of approaching a meta-analysis. An index of cognitive reserve in HIV was developed based on the relative benefits of various socio-behavioural indicators which build cognitive reserve. This served as a unique contribution of this thesis. The development of the index involved identification of the extent to which specific cognitively stimulating activities (other than education and occupation) were associated with the probability of having a high cognitive performance. This was accomplished in a large dataset acquired from a longitudinal Canadian study (N=856) contributing evidence towards this rather understudied area in HIV.

Contribution of Authors

This thesis was a substantial part of the Canadian longitudinal cohort study titled "*Understanding and Optimizing Brain Health in HIV Now*" (PI: Marie-Josée Brouillette, Lesley Fellows and Nancy Mayo). As supervisor, Dr. Mayo oversaw all aspects of the thesis. For the first manuscript with the meta-analysis, the data abstraction, statistical analysis and write-up were performed by the doctoral candidate under the thorough supervision of Dr. Mayo. Dr. Nandini Dendukiri provided her expertise in steering the statistical analysis for this work.

To the doctoral candidate's knowledge, an index derived from the unique contributions of various indicators of cognitive reserve in HIV was not available. Therefore, an index of cognitive reserve was developed and validated based on the dataset acquired from +BHN study (N=856). The statistical analysis and the write-up were carried out by the doctoral candidate under extensive direction of Dr. Mayo. The exercise regimen implemented in this thesis was delivered under the guidance of Dr. Mylene Aubertin and Dr. Mayo. The doctoral candidate made revisions to the ethics protocol, collected the data, ran the exercise intervention along with the certified trainers from the collaborating institution [Université du Québec à Montréal (UQAM)], analysed the data (N=27), and produced the manuscript under Dr. Mayo's supervision. Dr. Fellows and Dr. Brouillette provided professional insight and critical feedback on the subject areas addressed in the first three manuscripts. The fourth manuscript aligned with the conception of the exercise feasibility study and was the product of the 30-year anniversary of a rehabilitation journal (*Clinical Rehabilitation*). The data abstraction, data analysis and write-up of this manuscript was performed by the doctoral candidate under the direct supervision of Dr. Mayo. The rehabilitation-oriented feasibility studies were identified from a preceding study on clinical trials conducted in Dr. Mayo's lab. Vanessa Bouchard, Carolina Moriello and Dr. Sabrina Figueiredo provided feedback for the manuscript.

Thesis Organization and Overview

The thesis comprises four manuscripts in total, two of which have already been published in peer-reviewed scientific journals. In line with the Graduate and Postdoctoral Studies (GPS) regulations, an introduction and conclusion independent of the four manuscripts has been incorporated in it. In this context, it is important to mention that repetitiveness is inevitable in this work. A brief outline of the thesis is as follows.

Chapter 1 covers an overview of the neurocognitive deficits which have been observed in HIV and introduces the concept of cognitive reserve.

Chapter 2 covers the rationale which drove this thesis and lists the specific objectives addressed in the manuscripts.

Chapter 3 is the first manuscript titled, *"Association between cognitive reserve and cognitive performance in people with HIV: a systematic review and meta-analysis".* The main objective of this study was to estimate the strength of association between cognitive reserve and cognitive ability based on the published literature in HIV. The manuscript was published in the *Journal of AIDS Care* earlier this year.

Chapter 4 links the first manuscript with the second manuscript.

Chapter 5 is the second manuscript titled *"Development and validation of a cognitive reserve index in HIV (CRI-HIV)".* This work focused on developing an index of cognitive reserve based on the data acquired from Positive Brain Health Now (+BHN) study, which is a Canadian longitudinal study on HIV. An index was devised based on the unique contributions of specific indicators of cognitive reserve. It was validated against a performance-based measure of

cognitive performance and measures of everyday functioning. This manuscript has been submitted to *The Lancet HIV*.

Chapter 6 provides a link between the second and the third manuscript.

Chapter 7 covers the third manuscript titled "*Feasibility and potential for efficacy of a structured exercise programme in improving cognitive performance in HIV"*. This study evaluated the feasibility and efficacy potential of a 12-week combined aerobic and resistance training on cognitive performance in HIV. The sample for this study was identified from the parent cohort (+BHN). Adherence to the exercise schedule and acceptability of the exercise intervention was good, although the recruitment of participants was laborious. The intervention did not yield benefits on the primary outcome of efficacy potential of cognitive performance although benefits were observed on the measures of physical performance and exercise capacity in the intervention group.

Chapter 8 links the third and the fourth manuscript.

Chapter 9 is the fourth manuscript titled "*Where have all the pilot studies gone? A follow-up on 30 years of pilot studies in Clinical Rehabilitation"*. The specific objectives were to estimate the extent to which 191 feasibility studies in rehabilitation: (i) addressed needed objectives; (ii) led to definitive trials; and (iii) whether the subsequent undertaking of a definitive trial was influenced by the effect size observed. This study showed that only a trivial proportion of these studies were followed-up in a full-strength clinical trial. This work set out the key areas of focus for feasibility studies published in the field of rehabilitation.

Chapter 10 is an overall discussion and conclusion based on the previous chapters included in this thesis. It also addresses the important implications of this work.

Corresponding figures, tables and references are presented at the end of each manuscript. The references for the published manuscripts have been adapted to fulfil the journal requirements. The references for the first, second and last chapters have been provided at the end. The appendices include additional information that was not covered in the manuscripts and was deemed important in the context of this thesis.

Chapter 1: Background

Availability of treatment for seropositive individuals with combined anti-retroviral therapy (cART) has transformed Human Immunodeficiency Virus (HIV) from a potentially fatal disease to a manageable chronic condition (Clifford & Ances, 2013; Heaton et al., 2010). A meta-analysis showed that individuals who undertake advanced drug regime are likely to survive for more than 10 years even after the onset of Acquired Immunodeficiency Syndrome (AIDS) (Poorolajal et al., 2016). The medical attention in recent years has shifted from severe immunosuppression resulting from opportunistic infections to HIV-associated long-term complications including HIV-associated neurocognitive disorders (HAND) (Fettig et al., 2014; Kranick & Nath, 2012).

1.1 Epidemiological Portrait of HIV

HIV is a continuing international epidemic (Bourgeois et al., 2016). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS, 2017), there were 36.9 million people living globally with HIV. The most common subtype of HIV in North America is HIV-1 clade B, representing the majority of infections in the US (Tyor et al., 2013). The Public Health Agency of Canada (PHAC) estimated the prevalence of HIV at the end of 2016 was 63,110 with an overall 5% rise in the prevalence since the year 2014 (PHAC, 2018). Although Canada has a low prevalence of HIV, the epidemic is seen to a greater extent in certain segments of the population including homosexual men and indigenous people. The highest concentration of all new HIV infections in 2016 were reported in homosexual men (52.5%) (PHAC, 2018). Hornberger et al., (2010) estimated that 7.5 quality-adjusted life years (QALY) are lost when adults contract HIV

translating to a cost of $375,000 per person in Canada. (Kingston-Riechers & Canadian AIDS Society, 2012).

1.2 Natural History of HIV

Blood and bodily fluids of an infected person contain the virus, which can be typically transmitted via sexual contact, parenterally, perinatally or via breastfeeding. Infection with HIV results in the progressive destruction of CD4+ T lymphocytes (Harrison, 2018). The progression of HIV (without treatment) has been briefly outlined below and illustrated in Figure 1. *Of note, all participants studied in the second and third manuscript in this thesis were taking cART.*

a) Acute Infection Phase: Majority of individuals encounter extreme flu-like symptoms 2-4 weeks following the exposure to the virus. The symptoms can range widely from a mild, glandular fever-like illness to an encephalopathy. Often, the diagnosis is missed as non-specific symptoms during this phase are erroneously ascribed to causes other than HIV. The antibodies could take up to 12 weeks to reach seroconversion (Harrison, 2018).

b) Aysmptomatic HIV Infection/Clinical Latency: During this particular phase, the virus replicates at relatively low rates, and the infected individuals could remain well for around 10 years without needing drug therapy. Viral replication and plasma viremia are controlled by the immune response constituted by the CD4+ T cells (Harrison, 2018).

c) HIV Disease and AIDS: If left untreated, HIV progresses to AIDS. The infected individuals are profoundly immunosuppressed, and they are at an enormous risk of contracting opportunistic infections and tumours, with reduced life expectancy to as little as one year (Harrison, 2018).

1.3 HIV-Associated Neurocognitive Disorders (HAND)

Despite successful viral suppression, the post-cART era has been dominated by HIV- associated neurocognitive disorders (HAND). These range from milder and asymptomatic forms to severe dementia (Table 1), in which persistent infection in the central nervous system (CNS) plays a central role (Clifford & Ances, 2013). The estimates on prevalence of HAND often vary depending upon the study populations and techniques used to evaluate cognitive impairment. The prevalence rates fall between 20% to 70% (Saloner & Cysique, 2017). Based on the current rubric of HAND classification (Frascati criteria) (Antorini et al., 2007), the largest cross-sectional data from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study revealed cognitive decline in 814 (52%) of 1555 HIV participants (Heaton et al., 2010). Although the prevalence of HAND did not decrease with the advent of cART in 1996, the nature and severity of the disease has dramatically shifted (Saylor et al. 2016; Gelman, 2015). Moreover, as doctors and scientists navigate the novel landscape of HIV+ population over 50 years (Smith et al., 2010), combined effects of aging and HAND have been deemed to further complicate efforts toward precise diagnosis and treatment (Hellmuth et al. 2015). A decision-making process used for the diagnosis of HAND is illustrated in Figure 2.

1.3.1 Pathogenesis of HAND

Despite impressive systemic viral suppression, the brain acts as a sanctuary for viral replication which causes sustained neuroinflammation (Harezlak et al., 2011). Although there is meagre evidence that HIV directly infects neurons, it produces neuroinflammation and enters glial cells (i.e., macrophages and microglia) which are instrumental in maintaining neuronal health. As the glial cells get infected, they release neurotoxic viral proteins which trigger astrocyte activation. As a consequence, there is an increase in glutamate levels which lead to aberrant neurotransmission, synaptodendritic pruning and neuronal damage. CSF levels of glutamate have

been found to be 5 times higher in HIV+ individuals than healthy controls (Ferrarese et al., 2001). Micoglial activation also results in the release of inflammatory substances such as quinolinic acid and cytokines leading to oxidative stress and ultimately neuronal death (Saylor et al., 2016; Fields, 2009). Neuroimaging studies have demonstrated evidence of neuroinflammation through cortical thinning of the prefrontal cortices in HIV (Plessis et al., 2014). The neuropathogenesis of HAND is illustrated in Figure 3.

1.3.2 Predisposing Factors for HAND

Numerous risk factors have been associated with an augmented likelihood of developing HAND. Previous literature has revealed that older age and lower nadir CD4+ are linked with HAND (Victor & Paul, 2006). There is conflicting evidence on whether HIV accelerates the aging process or whether it propagates aging via additional predisposing factors (Wing, 2017; Pathai et al., 2014).

Several co-morbidities that could yield an adverse impact on the neuropsychological performance include diabetes, hypertension, medication toxicities, psychoactive substance abuse, hepatitis C co-infection and psychiatric disorders (Tedaldi et al., 2015).

1.4 Neurocognitive Profile of HAND

Not only HAND leads to adverse effects on medication adherence, ability to drive a motor vehicle, remembering medical appointments, management of finances, use of electronic devices such as computers and smartphones, and overall quality of life (Sanmarti et al., 2014; Thames et al., 2011; Ettenhofer et al., 2009; Marcotte et al., 2006; Heaton et al., 2004), it is also considered as a predisposing factor for mortality (Saylor et al., 2016; Sevigny et al., 2007).

The neuropsychological profile of HAND is characterized by impairments in speed of processing, psychomotor speed, executive functioning, and learning and memory reflecting

dysfunction in frontal-subcortical networks (Vance et al., 2013; Woods et al., 2009; Lojek & Bornstein, 2005). Various neurocognitive domains affected in HAND have been summarized in Table 2. A brief overview has been presented as follows.

1.4.1 Attention & Information Processing Speed

In the earlier stages of HIV, simple attention is relatively unaffected but mild-to-moderate difficulties are observed in the later stages (Reger et al., 2002). Complex attention measures, e.g., Paced Auditory Serial Addition Test (PASAT) (Marcotte et al., 1999) and Digital Symbol Test (Stern et al., 2001) and other specialized measures capturing divided or selective attention (Castellon & Hardy, 2000) have revealed poor performance among people with HIV (Grant, 2008). A bulk of research shows that HIV is linked with mild difficulties in fundamental attentional processes which get intensified when attentional load is increased (Hardy & Hinkin, 2002). Conventional neuropsychological tests of attention are non-specific and are often timed. They may also have a considerable overlap with speed of information processing (Levine et al., 2008). Deficits in processing speed and attentional skills can lead to impairment in other cognitive domains (Hardy & Hinkin, 2002). Although there are only a trivial number of studies which have examined speed of processing solely, it has been suggested that tasks of processing speed also exhibit a good sensitivity to HAND (Baldewicz et al., 2004).

1.4.2 Psychomotor Skills

Motor skills are at a disadvantage in people with HIV at an advanced stage. (Dawes et al., 2008; Rosca et al., 2012). Decline in motor performance has been linked with progression of HIV (Grant, 2008). Slowed performance in psychomotor activities, e.g., those involving rapid movements (Finger Tapping Test), or those requiring speed and fine motor co-ordination (as in commonly administered Grooved Pegboard Test), occur when psychomotor skills are affected

(Heaton et al., 1995; Reger et al., 2002). As psychomotor tests are relatively simple and less influenced by cultural factors, these are often employed in settings with time constraints and in international research (Grant, 2008).

1.4.3 Visuoperception

Visuospatial skills impart the ability to detect, manipulate, and integrate a visual stimulus in the context of its environment. Emerging evidence has shown that mild visuospatial deficits are present in people with HIV (Woods et al., 2009) although an earlier meta-analysis revealed mixed findings (Cysique et al., 2006). The nature and origin of the impairment is not very clear. It has been argued that connectivity of the basal ganglia to the dorsolateral prefrontal cortex, and posterior parietal lobes could lead to parietal lobe dysfunction and ultimately visuo-spatial dysfunction (Woods et al., 2013). Visual attention deficits may have negative repercussions in everyday life (for example, increased risk of automobile accidents) (Marcotte et al., 2006).

1.4.4 Verbal Language Skills

Language impairments are not classically a central feature of the early stages of HAND. However, they could arise due to other comorbidities (e.g. Alzheimer's disease) (Backman et al., 2003). If an aspect of language is impaired, it is likely to be performance on word generation tasks (such as fluency) (Grant, 2008). Rippeth et al. (2004) reported that 40% of their sample with HAND displayed evidence of verbal fluency impairment – a skill associated with frontostriatal systems and executive functioning. These impairments are usually mild in the initial stages but can be more pronounced in advanced HIV (Iudicello et al., 2007). Noun generation relies on temporoparietal networks and semantic memory stores, whereas verb production puts demands on frontal systems, executive functioning and motor planning. Action fluency (based on verbs) offers more ecological validity and sensitivity as compared to letter and

animal fluency (category fluency) in prediction of IADL dependency in HIV (Woods et al., 2006b).

1.4.5 Learning and Memory

Episodic memory deficits are frequently encountered in HIV; with prevalence estimates from 40% to 60% (Rippeth et al., 2004). These deficits are usually observed on verbal (e.g., word lists) and visual (e.g., simple and complicated design) activities. In combination with psychomotor slowing, these deficits are considered good predictors of HAND (Carey et al., 2004). A dimension of episodic memory that depends upon frontal systems is prospective memory, which is critical to independence in several IADL tasks, such as employment, financial management and medication adherence. Previous research has shown that evaluation of prospective memory provides ecological validity in the prediction of IADL deficits (Woods et al., 2008a, Woods et al., 2008b).

Heaton et al. (1995) showed that 50% of their sample in varying stages of HIV disease demonstrated difficulties in learning different types of information, including explicit and procedural information. Explicit memory involves learning focused on people, things, places, events, etc., whereas procedural memory entails learning of procedures or skills (such as bike riding) (Grant, 2008). Murji et al. (2003) have suggested that problems faced by HIV in new learning are the consequence of faulty executive coding rather than a deficit of memory formation. These are similar to difficulties seen in subcortical dementias (e.g., Parkinson's Disease).

1.4.6 Executive Functioning Skills

Executive functioning tasks have been linked to everyday functioning (Heaton et al., 2004) as they are instrumental in several situations (e.g. attention and arousal) while others are only

needed in specific situations (e.g. multitasking). 'Executive functioning' encompasses several intricate higher-order skills including mental flexibility, abstract reasoning, initiation, planning, decision-making, set-shifting (holding a number of tasks in mind), social behaviour, affect and motivation (Hodges, 2007). Using a cluster analysis, Dawes et al., (2008) revealed that executive functioning was central to most neurocognitive impairment profiles in HIV and recognized it as a predictor of functional capacity, vocational status and medication adherence in HIV (Walker & Brown, 2017). Also, it governs the processes that are required for sexual behaviour and risk reduction (Golub et al., 2012). People with HIV have been reported to have a tendency to select larger, immediate rewards over smaller ones gained gradually, reflecting more impulsivity leading to risky decision-making (e.g., choosing not to wear a condom) (Martin et al., 2004).

1.5 Cognitive Reserve

Cognitive reserve is a pivotal concept that stemmed from the disparity between the brain pathology and its clinical manifestations (Stern et al., 2018). It is defined as "the ability to make flexible and efficient use of cognitive networks when performing tasks in the presence of brain pathology" (Stern, 2002). Individuals with higher levels of cognitive reserve have a tendency to have better clinical outcomes (Steffener & Stern, 2012; Basso & Bornstein, 2000; Xu et al., 2015).

Another overlapping concept, called brain reserve, has been used interchangeably with cognitive reserve to account for the disjunction between the clinical presentation and neuropathology. Although the conceptual boundaries between cognitive and brain reserve are not always obvious, some of the distinct definitions suggest that brain reserve pertains to the structural aspects of brain quantified as brain volume, head circumference, synaptic count, or dendritic branching (Christensen et al., 2007; Valenzuela & Sachdev, 2006).

It is often categorized as a passive model (Figure 4) which assumes there is a fixed threshold of brain reserve – once it is exhausted beyond this threshold, clinical deficits begin to emerge. Also, it is quantitative; it assumes that a specific type of neurological insult will have the same impact on each individual and repeated neurological insults are additive (Stern, 2002). In contrast, cognitive reserve is an active model (Figure 5), implying that two individuals with the same amount of neurological insult to the brain may show a different profile of clinical or functional deficits. Also, the critical threshold at which the impairment occurs would vary from individual-to-individual depending upon how resilient the cognitive networks are in deploying the available neural substrate. Overall, cognitive reserve is how flexibly and efficiently an individual utilizes the available brain reserve in the face of a neurological insult (Leon et al., 2014; Satz et al., 2011).

A wide array of life exposures or experiences including educational attainment, occupational complexity, leisure activities, social engagement are considered as contributors to cognitive reserve (Stern, 2013). Additionally, cognitive reserve is believed to be a dynamic or malleable concept so lifestyle modifications even in later years could proffer protection against age or disease-related neuropathology (Stern, 2013). The clinical utility of cognitive reserve should not be underestimated as it could be instrumental in identifying people who are at risk for developing neurocognitive impairment.

1.5.1 Epidemiology of Cognitive Reserve

Stern et al., (1994) followed up 593 community dwelling, non-demented seniors over 60 years and found that risk of dementia was twice as high in seniors with low education (<8 years) in comparison to those with higher education [relative risk (RR) = 2.2; 95% confidence intervals (CI): 1.33 to 3.06]. Also, the likelihood of incident dementia was greater in those with lower lifetime occupational attainment (RR = 2.25; 95% CI: 1.32 to 3.84). Scarmeas et al., (2001)

reported that individuals who engaged more in leisure activities had 38% lesser risk of developing dementia. A systematic review (Valenzuela & Sachdev, 2007) highlighted that occupation, premorbid IQ, and engagement in cognitively stimulating activities had a protective effect on incident dementia [odds ratio (OR) = 0.54; 95% CI: 0.49 to 0.59].

Epidemiological evidence on cognitive reserve also comes from the aging literature where higher education or literacy has been associated with delayed cognitive or functional impairments (Chodosh et al., 2002; Albert et al., 1999). In a more recent study (Lenehan et al., 2015) using growth mixture modelling, 92.5% of 359 older adults (aged 50-79 years) who undertook a minimum of 1 year part-time or full time university education demonstrated a linear increase in cognitive reserve over 4 years compared to the controls (N=100) who did not engage in any tertiary level of education. It is theoretically believed that cognitive reserve develops in response to novel cognitively stimulating experiences across the lifespan of an individual (Stern et al., 2002). The aforementioned study (Lenehan et al., 2015) provided preliminary evidence on the dynamic nature of cognitive reserve.

1.5.2 Mechanisms Behind Cognitive Reserve

Two mechanisms have been posited to justify the concept of cognitive reserve: neural reserve and neural compensation (Stern, 2009). Neural reserve suggests that differential efficiency or capacity of brain networks may account for individual differences in their ability to withstand neuropathology. Networks that are more efficient and flexible could be capable of coping with disruption caused by a neurological insult. On the other hand, neural compensation refers to the inter-individual variations in the ability to compensate for neuropathology by recruiting alternate brain networks that are not usually employed in performing a task (Stern, 2009).

1.6 Measurement of Cognitive Reserve

Cognitive reserve is considered a hypothetical construct and its measurement is challenging (Jones et al., 2011). Previous researchers have employed socio-behavioural proxies or indicators based on epidemiological studies (Meng & D'Arcy, 2012). As affirmed by the white paper on cognitive reserve (Stern et al., 2018), education, occupation and IQ have been identified as the commonly employed proxies. Social support, bilingualism, engagement in physical activity and leisure activity has also been used to infer cognitive reserve (Stern et al., 2018; Sposito et al., 2015; Perquin et al., 2013; Scarmeas et al., 2003; Wilson et al., 2002; Scarmeas et al., 2001).

As cognitive reserve is conceptualized as a product of accumulation of various proxies, a single proxy is deemed insufficient to capture the entirety of the construct. Therefore, in recent years, multiple proxies have been used instead (Jones et al., 2011). Also, it is important to underscore the fact that each of the components of cognitive reserve could uniquely contribute to it. However, the summary measures of cognitive reserve frequently used in the previous research (Stern et al., 2018) do not account for differential contributions from different components. Measures that tap into the unique contributions are uncommon in the field of cognitive reserve. Other methods that are infrequently used to estimate cognitive reserve include functional imaging and 'residual' approaches. Reed et al (2011) quantified cognitive reserve as variance in episodic memory that remains after accounting for various demographic factors and structural brain alterations. This residual approach has been considered as a 'direct' measure of cognitive reserve (Stern et al., 2018). However, this approach has limitations as the methodology may hugely vary across studies due to differences in the selection of predictors and outcomes.

In this thesis, socio-behavioural proxies mentioned in the literature have been assumed to build the latent construct of cognitive reserve. This work has been carried out under the premise that this construct fits within a formative measurement model (Stern et al., 2018; Ravitch & Riggan, 2016; Edwards & Bagozzi, 2000). This has been illustrated in Figure 6.

1.7 Nomenclature of Cognitive Constructs

This thesis is conducted within the context of a large Canadian Institutes of Health Research (CIHR) funded team grant: Positive Brain Health Now (BHN) (Mayo et al., 2016). The investigators of +BHN identified that the nomenclature describing cognitive impairment and the ways in which cognition is measured varies across clinical disciplines posing a challenge in interdisciplinary research. For the purpose of this thesis, the term cognitive ability is used to denote a continuum rather than diagnostic classification, as denoted by the term cognitive impairment. To be consistent with nomenclature describing disability and function from the World Health Organization's International Classification of Functioning, Disability, and Health (ICF), the term measured or performance-based cognitive ability (shortened to cognitive performance) has been employed to reflect the domain of "impairment".

The term self-reported cognitive ability is used to represent difficulties that people experience with cognitive activities like remembering tasks to complete. This term is preferred over the term "cognitive symptoms or complaints" as it is compatible with the ICF terminology. In the context of this thesis, self-reported cognitive ability is used as a proxy for everyday functioning. From a broader perspective, the term brain health refers to a multi-dimensional construct reflecting the brain's role in cognition (measured performance and self-reported deficits), mood, motivation and energy (Mayo et al., 2016).

This chapter threw light upon the epidemiological features of HIV disease, HAND and its pathogenesis, and the neurocognitive profile encountered in HIV. Also, the concept of cognitive reserve, its indicators, mechanisms, and the key terminology employed in this thesis were introduced.

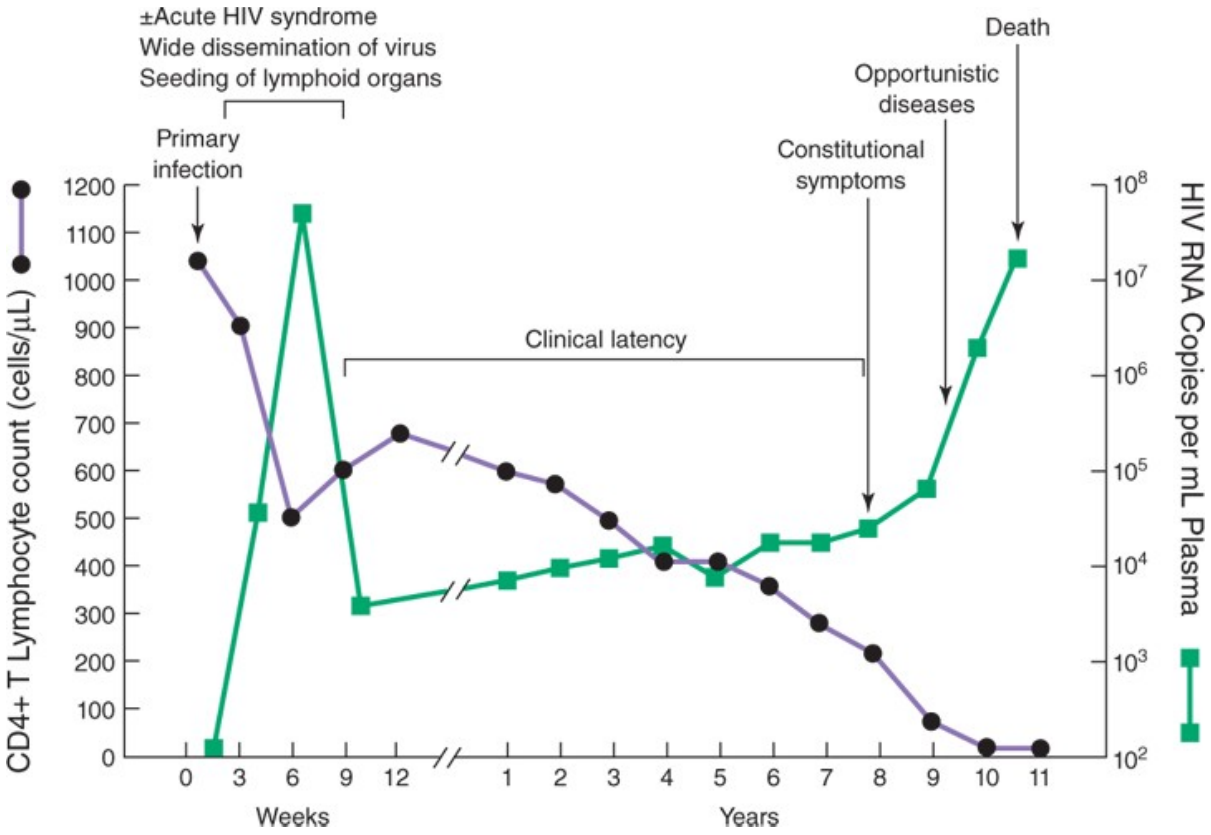

Figure 1. Natural History of HIV infection. The events that occur, in the absence of treatment, during the course of HIV from the primary infection through the development of advanced disease can be complex and varied (Reproduced from Harrison, 2018)

Table 1. Categories of HIV-Associated Neurocognitive Disorder (HAND), Frascati Criteria (Antorini et al., 2007)

	Neurocognitive Status[#]	Functional Status[*]
Asymptomatic Neurocognitive Impairment (ANI)	1 SD below mean, 2cognitive domains	No Impairment in activities of daily living
Mild Neurocognitive Disorder (MND)	1 SD below mean, 2cognitive domains	Impairment in activities of daily living
HIV Associated Dementia (HAD)	2 SD below mean, 2 cognitive domains	Marked impairment in activities of daily living

[#]Neurocognitive testing should include evaluating at least five domains including attention- information processing, language, abstraction-executive, complex perceptual motor skills, memory (including learning and recall) simple motor skills or sensory perceptual skills.
Appropriate norms must be available to determine the number of domains in which performance is below 1 standard deviation (SD).
[*]Functional status is typically evaluated by self-report but may be corroborated by a collateral source. No agreed upon measures exist for HAND criteria.

Of note, for HAND diagnosis other aetiology of dementia must be ruled out and confounding effect of substance use or psychiatric illness must be considered.

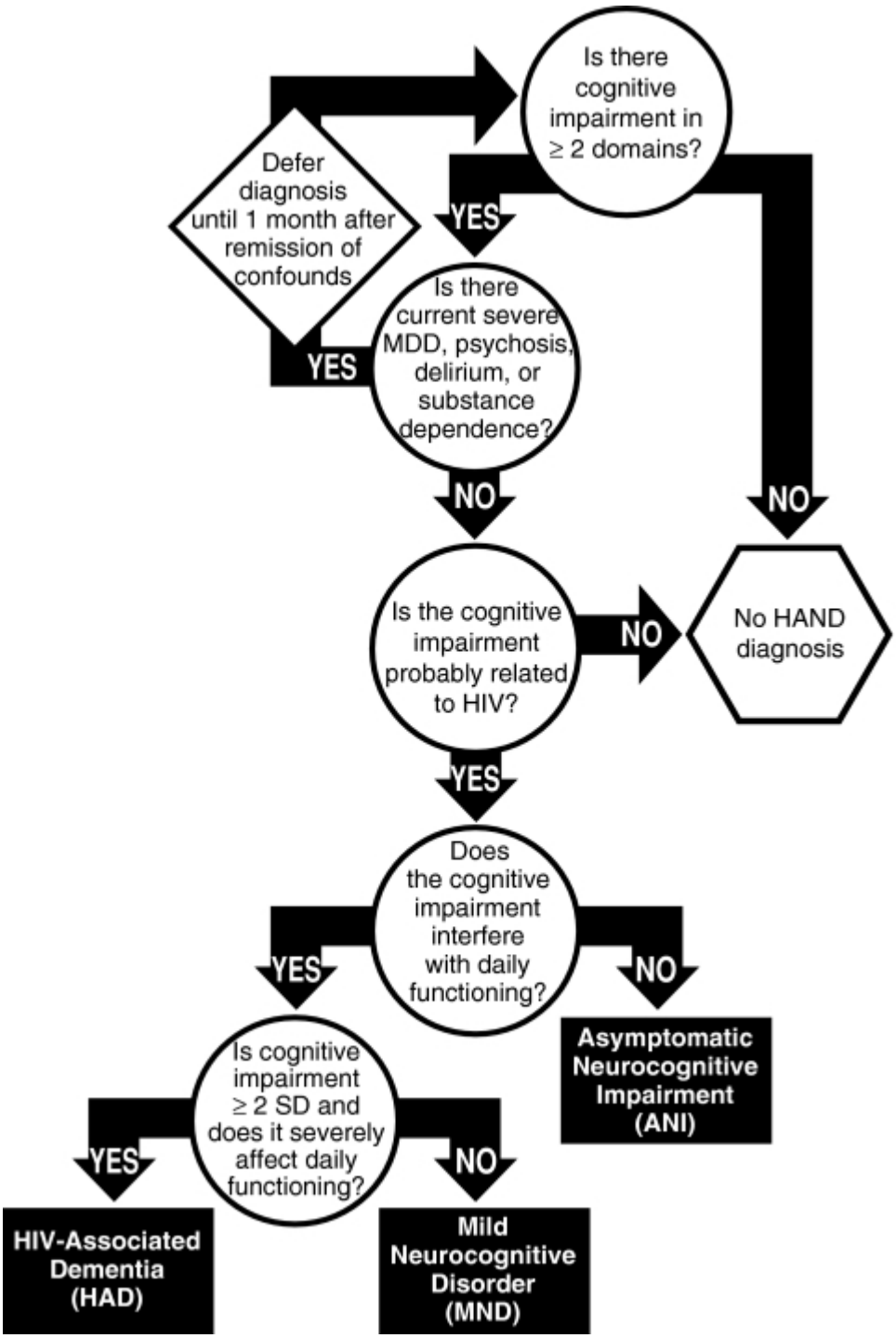

Figure 2. Proposed decision tree for the diagnosis of HAND (Reproduced from Woods et al., 2009)

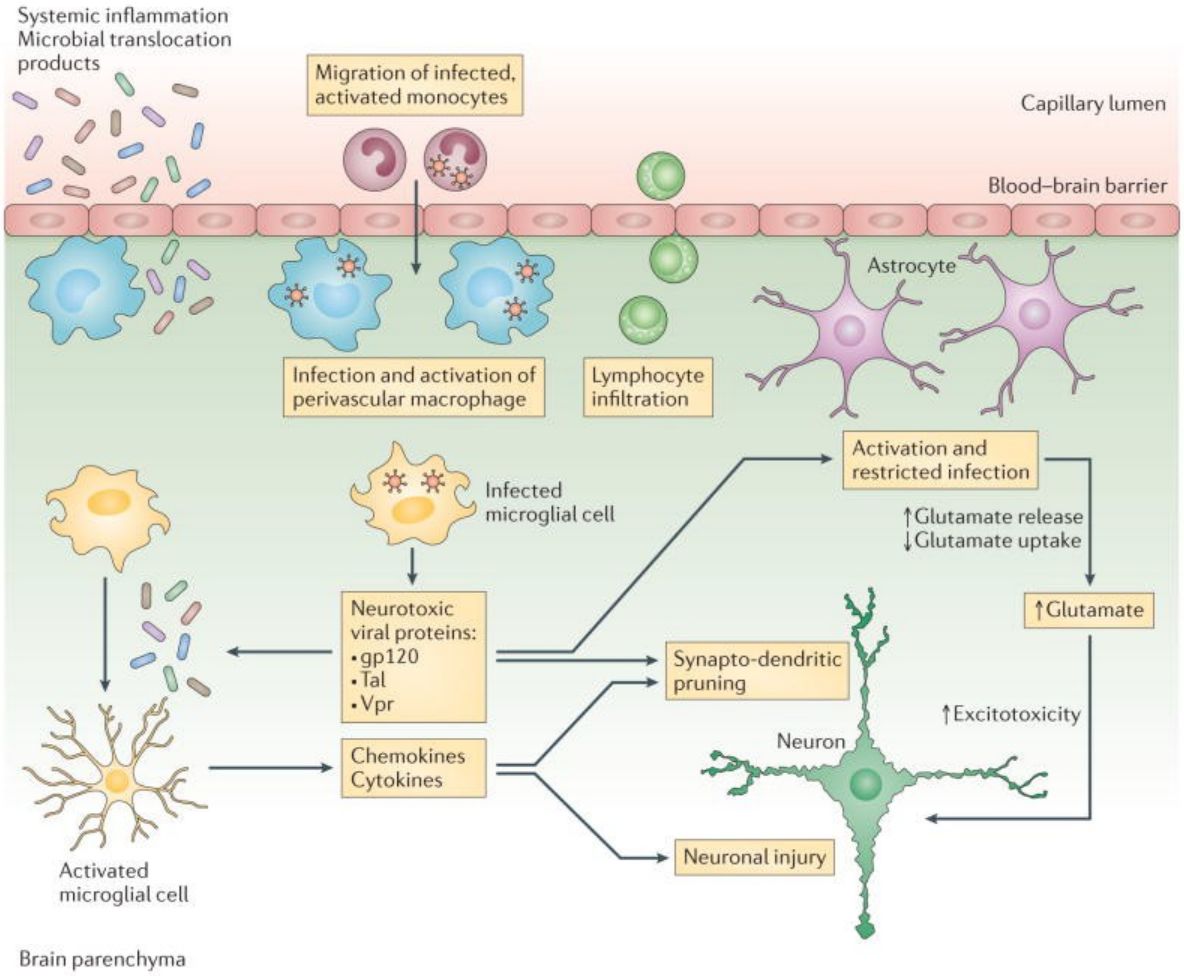

Figure 3. Neuropathogenic mechanisms that contribute to HIV-associated neurocognitive disorders (Reproduced from Saylor et al., 2016)

Table 2. Neurocognitive domains affected in people with HAND (Based on Woods et al., 2009)

Neurocognitive Domains	Associated impairments in HAND
Attention, speed of processing and working memory	Complex information manipulation, especially under time pressure Visual search and discrimination Covert orienting Divided or selected attention Visual and verbal working memory
Learning and memory	Episodic memory deficits on visual and verbal tasks; consistent with a mixed encoding and retrieval profile Learning stories and lists Non-verbal learning; complex designs Time-based prospective memory tasks
Verbal language abilities	Verbal fluency, e.g., spontaneous generation of words or other language, particularly under pressure of time (on both action and categorical fluency tasks)
Executive functioning	Abstraction Novel problem solving Set-shifting Response inhibition Risky decision-making
Psychomotor abilities	Bradykinesia and bradyphrenia Reduced coordination Severe movement disorders are infrequent

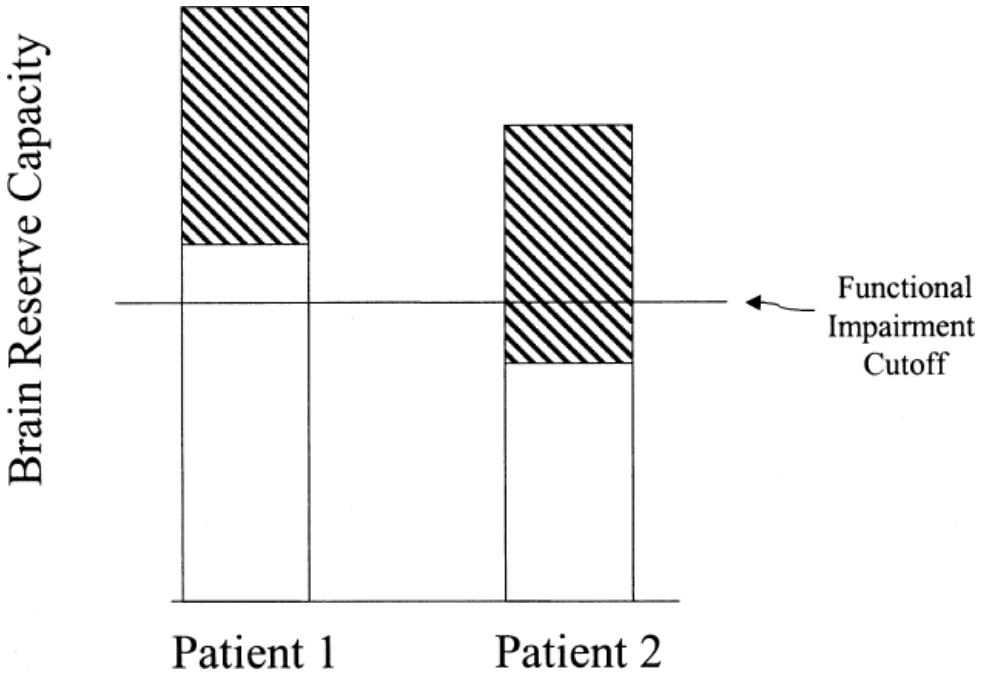

Figure 4. Passive nature of brain reserve. In two patients with varying levels of brain reserve, a lesion of particular size leads to a clinical deficit in Patient 2 who has lesser amount of brain reserve as it exceeds the critical threshold of brain damage sufficient to produce that deficit. (Reproduced from Stern, 2002)

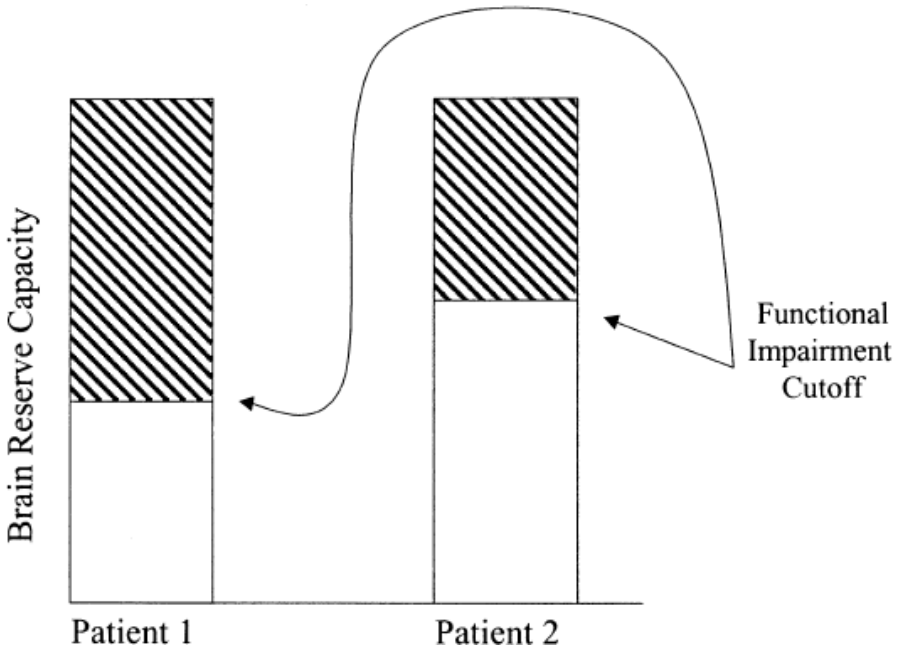

Figure 5. Active nature of cognitive reserve: Two patients have the same level of brain reserve. However, Patient 1 has higher cognitive reserve than Patient 2. Patient 1 uses more efficient processing mechanisms and is believed to tolerate a larger lesion than Patient 1 before functional impairment is evident. (Reproduced from Stern, 2002)

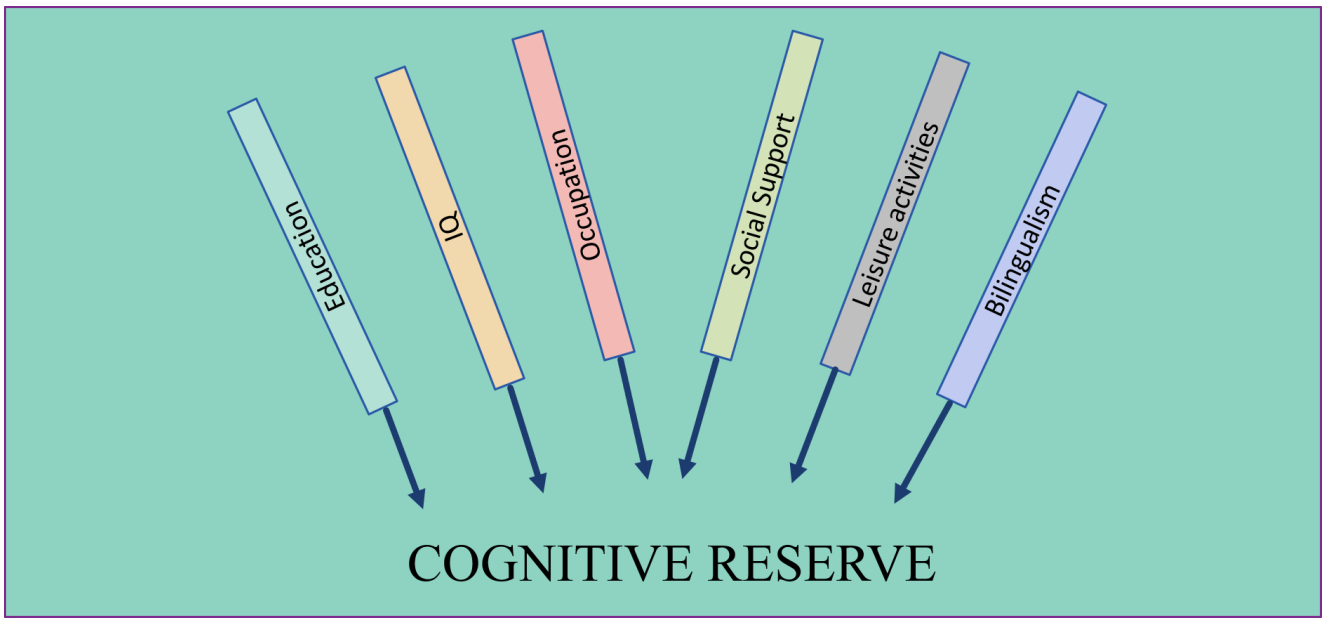

Figure 6. Indicators that build cognitive reserve (formative model)

Chapter 2: Rationale behind the Thesis

Neurocognitive impairments are of concern to people with HIV, but no two individuals are affected alike. The hypothetical concept of cognitive reserve has been posited to justify why two individuals could present with varying clinical manifestations despite having similar levels of neuropathology (Stern, 2012). Cross-sectional and longitudinal studies have suggested that individuals with greater cognitive reserve may have more neuronal resources available to safeguard them from cognitive impairment (Lojo-Seoane et al., 2018). It is believed that cognitive reserve could potentially confer benefits by delaying the manifestations of brain pathology on cognitive performance (Stern, 2009). This concept could be utilized in addressing the challenges associated with HIV-associated neurocognitive disorders (HAND). The foremost component of this thesis was to estimate the strength of association between cognitive reserve and cognitive performance based upon the research published in the neuroHIV literature.

The protective effect of cognitive reserve on cognitive performance has received increasing attention in the last one decade. However, measurement challenges surrounding this latent construct have surfaced (Jones et al., 2011). Various socio-behavioural indicators, including educational level, occupational complexity, IQ, engagement in physical, social and intellectually stimulating activities have been inconsistently applied as either stand-alone or combined proxies of cognitive reserve (Stern, 2012). More recently, various proxies of cognitive reserve have been integrated into building indices in some non-HIV populations (Nucci et., al 2011; Valenzuela & Sachdev, 2007). Considering the mediating role of cognitive reserve between neuropathology and cognitive ability, it is important to parsimoniously account for the effects of cognitive reserve. Developing an index of cognitive reserve based on the differential contributions of specific proxies was the second component in this thesis.

Cognitive reserve is an important construct from a rehabilitation perspective, not only to understand variation in the effects of neuropathology, but also as a potentially amenable and accessible target of interventions (Vance et al., 2013). One common rehabilitation approach involves exercise. Exercise has been shown to have a direct, albeit small, effect on cognitive performance in other clinical and non-clinical populations (Ohman et al., 2015; Kelly et al., 2014). Exercise has also been hypothesized as a contributor to cognitive reserve (Sposito et al., 2015). Therefore, the third component of this thesis investigated the benefit of combined aerobic and resistance exercise training on cognition among people with HIV. A full-scale trial could not be justified based on the previous literature (O'Brien et al., 2016), thus a feasibility study was undertaken. Feasibility and pilot studies are notorious for leading nowhere (Shanyinde et al., 2011) so additional research was simultaneously conducted to identify limitations in such studies of rehabilitation type interventions in order to optimize the feasibility study presented here. This was the fourth and last part of the thesis.

2.1 Specific Objectives

The global aim of this thesis was to contribute evidence as to the role of cognitive reserve in protecting cognitive ability in people with HIV.

The specific objectives were as follows:

1. To estimate from the extant literature the strength of association between cognitive reserve and cognitive performance in people with HIV ***(Manuscript I).***

2. To develop an index of cognitive reserve for people living with HIV based on combining multiple indicators of cognitively stimulating lifetime experiences into a single value ***(Manuscript II).***

3. To estimate the feasibility and efficacy potential of a structured exercise program in improving cognitive ability, physical performance, and other indicators of brain health in HIV ***(Manuscript III).***

4. To estimate the extent to which pilot trials in the field of rehabilitation have been conducted with rigour and with maximum benefit to developing definitive trials ***(Manuscript IV).***

The following chapter will present the first manuscript that addresses the first objective of this thesis.

Chapter 3: Manuscript I

Association between cognitive reserve and cognitive performance in people with HIV: a systematic review and meta-analysis

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Association between cognitive reserve and cognitive performance in people with HIV: a systematic review and meta-analysis

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ABSTRACT

Cognitive reserve is a potential explanation for the disparity between brain pathology and its clinical manifestations. The main objective of this study was to estimate, based on published studies, the strength of the association between cognitive reserve and cognitive performance in individuals with HIV. A systematic literature search using Ovid MEDLINE, PsychINFO, and EMBASE was performed to identify studies published between 1990 and 2016 that quantified the association between cognitive reserve and cognitive performance in HIV. A random-effects meta-analysis was used to compute a summary estimate (Cohen's *d*) with 95% confidence intervals (CI) and 95% prediction intervals (PI). The risk of bias and quality of reporting in the studies were indicated by the Appraisal tool for Cross-Sectional Studies (AXIS). Ten observational studies were deemed eligible. The pooled effect size was 0.9 (95% CI: 0.7–1.0; 95% PI: 0.4–1.4) with marked heterogeneity studies [Cochran's Q ($df = 9$) = 28.0, $p = .0009$; I^2 statistic = 67.4%]. Risk-of-bias appraisal showed that non-response bias was never addressed and the items associated with selection bias were only partially met. The association between cognitive reserve and cognitive performance suggests that building reserve through non-pharmacological interventions could be a potentially effective way of combating cognitive impairment in people with HIV.

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KEYWORDS
HIV; cognitive reserve; cognitive ability

Background

The concept of cognitive reserve pertains to "the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult" (Stern et al., 2018). This definition comes from a "white paper" on the topic that harmonizes definitions from other authorities (Barulli & Stern, 2013; Umarova, 2017; Wang, MacDonald, Dekhtyar, & Fratiglioni, 2017). An individual with higher cognitive reserve will express less cognitive decline as compared to someone with lower reserve in the face of a similar extent of neuropathological burden (Stern, 2009; Thames et al., 2011). However, the mechanisms underlying cognitive reserve are not clear, and the construct itself is likely latent (i.e., can't be measured directly) (Clare et al., 2017; Jones et al., 2011; Satz, Cole, Hardy, & Rassovsky, 2011).

The current practice is to infer the degree of cognitive reserve from multiple proxies or indicators including educational attainment, occupational complexity, and past experiences (Stern, 2013). However, these proxies have been inconsistently employed across studies (Stern, 2013). Lack of specific indicators of cognitive reserve and lack of consistency in choice of indicators limits the validity of cognitive reserve as a construct for research and clinical purposes. A statistical approach has also been proposed, termed "residual approach", based on fitting a statistical model to a measure of cognition and inferring that the unexplained variance is cognitive reserve (Reed et al., 2010). This approach depends on the predictors and outcome measure specified in the model. In recent years, combining multiple indicators has been preferred over using a single indicator to represent cognitive reserve (Jones et al., 2011).

It is also not clear whether cognitive reserve is an endowment gained early in life, or reflects ongoing plasticity, making it a potential target for intervention in mid- or late-life. There is now emerging evidence that lifestyle modifications including physical, social and leisure activities even in later years could offer protection against age or disease-related neuropathology (Cheng, 2016; Stern, 2013; Valenzuela & Sachdev, 2007).

The bulk of cognitive reserve research has focused on aging (Tucker & Stern, 2011; Wilson, Barnes, & Bennett,

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2003) and health conditions affecting the brain including Alzheimer's disease (Scarmeas et al., 2003), multiple sclerosis (Benedict, Morrow, Weinstock, Cookfair, & Schretlen, 2010) and traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003). The impact of cognitive reserve on cognitive performance has been studied in HIV (Morgan et al., 2012), but not systematically. Combined antiretroviral therapy (cART) has revolutionized the care of people with HIV, who are now surviving to experience the effects of aging in addition to living with a chronic disease (Cody & Vance, 2016). As a consequence, the most severe form of cognitive impairment, HIV-associated dementia (HAD), has decreased from 10% to 15% in the pre-cART era (Janssen, Nwanyanwu, Selik, & Stehr-Green, 1992) to only 2% in the post-cART era (Heaton et al., 2010). Amongst those currently living with HIV, a high proportion (estimated at around 50%) exhibit milder signs of neurocognitive impairment (Cysique et al., 2009; Heaton et al., 1995; Robertson et al., 2007). Why do some people develop cognitive impairment even with well managed HIV, while others do not? In addition, some with cognitive impairment demonstrated on neuropsychological tests exhibit limitations in everyday functioning, while others with the same degree of impairment do not. These are the questions that are now important to address (Sacktor et al., 2001; Woods, Moore, Weber, & Grant, 2009). The need to untangle some of this variation in neurocognitive profile has sparked interest in better understanding the impact of cognitive reserve in people living with HIV (Foley et al., 2012; Morgan et al., 2012; Pereda et al., 2000).

While there is an existing literature on cognitive reserve and HIV, it has not yet been summarized systematically. Evidence of association between cognitive reserve and cognitive ability could encourage identification of individuals with low cognitive reserve who might be at higher risk of developing cognitive impairment. It might also point the way to new interventions to protect against cognitive decline. Therefore, the aim of this study was to estimate, through a systematic review of the literature, the strength of the association between indicators of cognitive reserve and cognitive performance in individuals with HIV.

Methods

The design and reporting of this systematic review and meta-analysis was informed by Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). No previous review in the same area was found in the Database of Abstracts of Reviews of Effects (DARE).

Search strategy for pertinent literature

The bibliographic search was carried out under the guidance of a qualified librarian and executed in three electronic databases: Ovid MEDLINE (1996–2016), EMBASE (1996–2016) and PsychINFO (1996–2016). The detailed search strategy for the Ovid MEDLINE database is given in Table 1. The search strategy included the phrase "brain reserve" as this term is sometimes used interchangeably with cognitive reserve.

Selection of eligible studies

After eliminating duplicate records from the database search, titles and abstracts were screened against the eligibility criteria.

Inclusion criteria: Articles that included HIV seropositive participants and provided quantitative data on the association between cognitive reserve and cognitive ability were deemed eligible. Only full-text English language publications with human participants were included. As the effect of cognitive reserve on cognitive ability was the parameter of interest, cognitive reserve had to have a specific definition or formulation that could be described.

Exclusion criteria: Grey literature including conference abstracts and dissertations was not considered for this review. Articles with no clear definition of cognitive reserve were eliminated, and literature reviews on cognitive reserve were deemed ineligible.

The records which fulfilled eligibility criteria were then subjected to full-text screening. The reference lists of the retrieved citations were scanned manually to locate further relevant articles. This process was accomplished by one reviewer (NK). Any queries regarding the choice of articles were discussed with a senior reviewer (NM).

Table 1. Specific search terms used in Ovid MEDLINE.

(1) exp HIV Infections/
(2) HIV Long-Term Survivors/
(3) hiv.ti.
(4) 1 or 2 or 3
(5) cognitive reserve.tw,kf
(6) brain reserve*.tw,kf.
(7) neurocognitive reserve.tw,kf.
(8) neuroresilience.tw,kf.
(9) neural reserve.tw,kf.
(10) neural resilience.tw,kf.
(11) cognitive resilience.tw,kf.
(12) neural compensation.tw,kf.
(13) cognitive stimulating activit*.tw,kf.
(14) neural efficiency.tw,kf.
(15) neural protection.tw,kf.
(16) neuroprotection.tw,kf.
(17) 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
(18) cognitive performance.tw,kf.
(19) cognitive impairment.tw,kf.
(20) cognitive ability.tw,kf.
(21) cognition.tw,kf.
(22) 18 or 19 or 20 or 21
(23) 4 and 17 and 22

Data extraction from eligible records

For each publication included, the following data elements were extracted: reference, geographic setting, sample size, operational criteria of cognitive reserve, primary outcomes with total number and parameters of effect size. The hypothesized relationships were also summarized, presented in the form of a statistical model. The data extraction process was completed by one reviewer (NK) and then reviewed by the senior author (NM).

Estimators of association

The optimal estimator of association in this context is Cohen's *d* (i.e., the standardized mean difference) where the outcome is expressed as a mean of a continuous variable and the exposure, here cognitive reserve, is binary (high/low). As each study presented different kinds of effect parameters (e.g., odds ratios, means and standard deviations), harmonization across studies was deemed essential to derive a common metric of effect size (i.e., Cohen's *d*). To facilitate meta-analysis, we derived Cohen's *d* for each study using the formulae published in the literature (Borenstein, Hedges, Higgins, & Rothstein, 2009; Friedman, 1968; Thalheimer & Cook, 2002) (Table 2). The precision of effect size was also estimated deriving a standard error (SE) of Cohen's *d* using the formula recommended by Hedges and Olkin (1985) (Equation 1).

Equation 1. Formula used for the estimation of standard error of effect size.

$$se = \sqrt{\frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2)}}$$

where *se* is the standard error, n1 is the sample size of one group, n2 is the sample size of the second group and *d* is Cohen's *d* (Hedges & Olkin, 1985).

Risk of bias and quality assessment

The appraisal tool for Cross-Sectional Studies (AXIS tool) was used to indicate the methodological quality and risk of bias for each study (Downes, Brennan, Williams, & Dean, 2016). The study appraisal was initially conducted by one reviewer (NK) and any problem areas were discussed with the senior reviewer (NM). In addition to the 20 items addressed by the checklist, an additional item was incorporated to address whether confounders were adjusted for in each study. Of these 20 + 1 items, items 5, 6, 7, 9, 13, 14 and 20 + 1 indicate the sources of bias possibly affecting the estimators of association. Items that were met were indicated by a closed circle, items unmet by an open circle, items partially met by a half moon and items whose status is unclear by "?".

Statistical approach

A meta-analysis was conducted using the *metafor* package within the R 3.4.2 software program (Viechtbauer, 2010) to compute the pooled summary estimate for the association between cognitive reserve and cognitive ability in terms of Cohen's *d*. As heterogeneity in the effect size was anticipated across the selected studies due to extensive variation in their methodology, the random-effects model was chosen *a priori*. The meta-analysis provided an overall estimate of effect and 95% confidence intervals (CI). In addition to the 95% CI, a 95% prediction interval (PI) (IntHout, Ioannidis, Rovers, & Goeman, 2016) was also computed. To detect statistical heterogeneity, Cochran's *Q* test was complemented with the I^2 statistic (Borenstein et al., 2009). Cochran's *Q* statistic reduces the question of heterogeneity to a dichotomy (Cochran, 1954). As it tends to have low power, its critical value was set at 0.1. On the other hand, the I^2 statistic is a measure of the proportion of variability between studies which is due to heterogeneity rather than chance (values of 25%, 50% and 75% were considered to reflect low, medium and high heterogeneity, respectively) (Higgins & Thompson, 2002).

To detect the risk of publication bias, a funnel plot was created plotting estimated effect sizes for each study against their standard errors. Egger's weighted regression test was also used to statistically assess publication bias.

Table 2. Formulae applied to derive effect size and its variability based on specific parameters available in the selected studies.

Parameter reported in the articles	Formula used to derive effect size (Cohen's *d*) and its standard error (SE_d)
Odds ratio (OR)	$d = \text{LogOR} \times \sqrt{3} \div \pi$ where π is the mathematical constant (approximately 3.14159) (Borenstein et al., 2009)
F-statistic	$d = \sqrt{\left\{F\frac{(n_1+n_2)}{n_1 n_2}\frac{n_1+n_2}{n_1+n_2-2}\right\}}$, where *F* is the *F*-statistic, n_1 is the number of subjects in the treatment group and n_2 is the number of subjects in the control group (Thalheimer & Cook, 2002)
t-Statistic	$d = 2t \div \sqrt{(n-2)}$ where *t* is the *t*-statistic and *n* is the total number of subjects (Thalheimer & Cook, 2002)
Correlation coefficient (*r*)	$d = 2r \div \sqrt{(1-r^2)}$ where *r* is the correlation (Friedman, 1968)

Results

Citation retrieval

The electronic database search identified a total of 259 records. After elimination of duplicate records, initial screening of titles and abstracts and full-text review of the remaining articles, 10 studies were included for comprehensive data extraction. The study selection process is shown in Figure 1.

Table 3 summarizes the study characteristics including reference, geographic setting, sample size, operational criteria of cognitive reserve, primary outcomes with total number and effect size estimator employed in each study. All studies were conducted either in Europe or North America. The sample size across the studies ranged from 26 to 366 with a median value of 75. All studies presented cross-sectional data except Basso and Bornstein (2000), who looked at the effect of premorbid IQ on measures of executive functioning taken twice across 12 months. Two studies presented binary outcomes: HAND status (Morgan et al., 2012), or cognitive ability dichotomized as high or low (Milanini et al., 2016). A variety of parameters of effect size were given by different authors: means and standard deviations, *F*-statistic, Cohen's *d*, and correlation coefficient were all presented once each, whereas *t*-statistics were the most frequently presented. Only four studies computed a global neuropsychological score and the rest provided effect parameters for individual tests which we averaged to produce a global score per study. Cognitive reserve was operationalized using inconsistent indicators. Among indicators of cognitive reserve, education and verbal IQ were most frequently used across the studies. Methods for adjusting for covariates varied by study. We grouped covariates into four domains: demographic (age and sex), HIV related, psychiatric and other variables in Table 3.

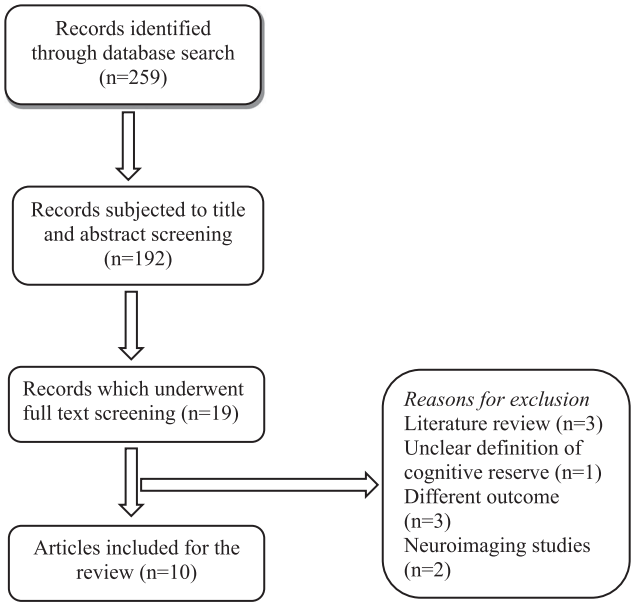

Figure 1. Flowchart of study selection process.

Critical appraisal of individual studies

The results of quality assessment for each study are shown in Table 4. For ease of presentation, each of the 21 items is sequentially numbered as in the AXIS, checklist. Across all studies, eight items (1, 2, 8,11, 12, 15, 16, 17 and 21) were consistently met; of these, only item 8 refers to a source of bias (i.e., information bias), two items (7, 14) were consistently unmet both of which indicate non-responder bias; two items (5, 6) were only partially met indicating likelihood of selection bias and another item (i.e., item 13) concerning non-responder bias was unclear across all studies. The remaining items (3, 4, 10, 17–19) refer to optimal methods of reporting rather than bias. Overall, there was little variation among the studies based on the risk of bias. The majority of studies were affected by selection bias and non-responder bias.

Summary effect and heterogeneity

On the basis of 10 associations yielded by the reviewed observational studies, the pooled effect size as per random-effects meta-analytic approach was 0.9 (95% CI: 0.7–1.0). The corresponding forest plot is depicted in Figure 1 with the studies ordered by magnitude of effect size. There was high (I^2 statistic = 67.4%) and statistically significant heterogeneity across studies [Q (df = 9) = 28.0, p = .0009]. Because of the high degree of heterogeneity, prediction intervals are also presented and were found to be much wider than the confidence intervals estimated for the summary effect (95% PI: 0.4–1.4). There was no evidence of publication bias as shown by the funnel plot in Figure 2 or the result of Egger's test (p = .7).

Discussion

The main objective of this systematic review was to estimate the strength of the relationship between cognitive reserve and cognitive ability in individuals with HIV. To the best of our knowledge, this is the first quantitative synthesis addressing this topic. Data from 10 studies were pooled (see Figure 1) and led to a summary effect size (Cohen's *d*) of 0.9 (95% CI: 0.7–1.0) with wide prediction interval (95% PI: 0.4–1.4). Because of the high degree of heterogeneity across studies, PI better

Table 3. Key characteristics of the articles included in the review.

Reference [Country]	Total sample size (*N*)	Primary outcomes [*n* outcomes]	Operational definition of cognitive reserve and scoring	Effect size estimator [Value]	Cohen's *d*
Foley et al. (2012) [U.S.A.]	77	Global cognitive ability score [1]	Word-reading ability[a] and education Sample-standardized values were averaged to form a composite score	*t*-Statistic [5.83]	1.3
Statistical model for the aforementioned study: Global cognition = Cognitive reserve + Age + Psychiatric functioning + (HIV related: 1 HIV status) + (Others: 1 psychosocial status)					
Pereda et al. (2000) [Spain]	100	Global cognitive ability score [1]	Verbal IQ[b], education and occupation[c] Rank values of the above measures were summed to derive a score	*t*-Statistic [3.994]	0.8
Low neuropsychological "Z" score = Cognitive reserve (high; low) + Age + Gender + (HIV related: 7)					
Patel et al. (2013)	366	Global cognition [1]	Word-reading ability[d] and years of education attained Standardized scores of the above were averaged to form a cognitive reserve score.	Wide range of *t*-statistics provided	1.0
Cognitive ability = Cognitive reserve + (HIV related: 1 disease severity) + (Others:3)					
Basso and Bornstein (2000) [U.S.A.]	155	Impairment Index [1]	Estimated premorbid WAIS-R Full Scale IQ[e] were computed using a regression equation	*F*-statistic [17.54]	0.8
Impairment Index = Premorbid IQ + (HIV related: 1 HIV status) + Time					
Stern, Silva, Chaisson, and Evans (1996) [U.S.A.]	75	Verbal learning and memory, and selective attention [2]	Verbal IQ[f], education, occupation[g] Rank values of the above measures were summed to derive a score	Mean and SDs [ES averaged to get a summary effect for three outcomes]	1.3
Cognitive ability (verbal learning and selective attention) = Cognitive reserve (high; low)					
Fazeli et al. (2014) [U.S.A.]	58 [48% with HAND]	Cognitive ability (global score) [1]	Verbal IQ[a] and education No score computed	Cohen's *d* [1.3]	1.3
Cognitive ability (continuous) = Active lifestyle factors (highest to lowest)					
Alvarez-Tostado, Inozemtseva, Aguiñiga, López, and Matute (2016) [Mexico]	26	Various neuropsychological tests [18]	Verbal IQ[c] and education Rank values of the above measures were summed to derive a score	Correlation [ranged from 0.03 to 0.83]	0.4
Cognitive ability = Cognitive reserve (high; low)					
Morgan et al. (2012) [U.S.A.]	33 [100% with HAND]	Sub-syndromic HAND and syndromic HAND (No HAND category excluded from analysis)	Verbal IQ[h], education, and occupation[i] Score calculated as an average of three sample-based *z*-scores	OR [3.17]	0.6
HAND status = Cognitive reserve + (HIV related: 1 AIDS) + (Psychiatric: 1 depression)					
Milanini et al. (2016) [Italy]	60 [40% with HAND]	High cognitive ability and low cognitive ability	Premorbid intelligence[j] and quantity of cognitive reserve accumulated by individuals throughout their lifespan measured using Cognitive Reserve Index (Nucci, Mapelli, & Mondini, 2012); effects presented per unit score, transformed by research team based on the specified dichotomy: <70 for low cognitive reserve	OR [15.21]	1.5
Cognitive ability = Cognitive reserve + Age + Sex + Education + HIV related variables: 12 + Others: 3					
Vázquez-Justo, Blanco, Vergara-Moragues, Gestoso, and Pérez-García, (2014) [Spain]	123	WAIS digital symbol, Trails A, Verbal fluency, WCST perseverative errors and WCST perseverative responses [5]	Verbal IQ[c] and education Score calculated by taking mean of standardized scores	Wide range of *t*-statistics provided	0.7
Cognitive ability (each of 5 neuropsychological tests) = Cognitive reserve score + Age + Socioeconomic status					

[a]Wide Range Achievement Test (WRAT) – Third Edition, Reading subtest.
[b]PRESCA Scale.
[c]Wechsler Adult Intelligence Scale (WAIS) Vocabulary subtest.
[d]American National Adult Reading Test (AMNART).
[e]Wechsler Adult Intelligence Scale (WAIS) full scale IQ.
[f]Vocabulary subtest of the Shipley–Hartford Institute of Living Scale.
[g]Stevens and Cho's Socioeconomic Index.
[h]Wechsler Test of Adult Reading (WTAR).
[i]Hollingshead score.
[j]Brief Intelligence Test (TIB).

Table 4. Findings of critical appraisal of the included studies using AXIS tool.

Reference Items[a]	Consistent ratings across studies 1, 2, 8, 11, 12, 15,16, 17, 21	Variation in ratings across studies 7, 14	13	5,6	3	4	9	10	18	19	20
Fazeli	●	○	?	●	○	?	◐	●	●	●	●
Morgan	●	○	?	●	○	○	○	●	●	●	○
Foley	●	○	?	●	○	●	●	○	○	●	○
Patel	●	○	?	●	○	●	●	○	●	●	○
Milanini	●	○	?	●	○	○	●	?	●	●	●
Pereda	●	○	?	●	○	●	●	●	?	●	●
Vazquez-Justo	●	○	?	○	●	●	●	●	●	●	●
Basso	●	○	?	○	○	○	●	●	●	●	●
Alvarez-Tostado	●	○	?	○	○	○	●	●	●	●	●
Stern	●	○	?	○	○	●	●	●	●	?	●

● Yes, ○ No, ◐ Partially done,? Not Clear

[a]1 Were the aims/objectives of the study clear?
2 Was the study design appropriate for the stated aim(s)?
3 Was the sample size justified?
4 Was the target/reference population clearly defined? (Is it clear who the research was about?)
5 Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?
6 Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?
7 Were measures undertaken to address and categorize non-responders?
8 Were the risk factor and outcome variables measured appropriate to the aims of the study?
9 the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted or published previously?
10 Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., *p*-values, confidence intervals)
11 Were the methods (including statistical methods) sufficiently described to enable them to be repeated?
12 Were the basic data adequately described?
13 the response rate raise concerns about non-response bias?
14 If appropriate, was information about non-responders described?
15 Were the results internally consistent?
16 Were the results presented for all the analyses described in the methods?
17 Were the authors' discussions and conclusions justified by the results?
18 Were the limitations of the study discussed?
19 Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?
20 Was ethical approval or consent of participants attained?
21 Was there an adjustment of confounders made?

illustrates the uncertainty in the summary effect. The PI indicates that in 95% of future similar studies, effect sizes between 0.4 and 1.4 are likely to be observed .

While we did not find any previous meta-analysis linking cognitive reserve and cognitive performance in HIV, this has been a frequently studied topic in the healthy aging literature. A recent meta-analysis of 135 studies of healthy older adults found modest associations ($r = 0.34$) between measures which combined individual proxy measures of cognitive reserve and cognitive domains. Also, small associations were observed between engagement in leisure activities, occupational attainment and cognitive performance (Opdebeeck, Martyr, & Clare, 2016). Our meta-analysis found strong associations between the indicators of reserve and cognitive performance ($d = 0.9$). However, converting this effect size to a correlation would yield a value of 0.36 which is close to the one observed by Opdebeeck et al. (2016).

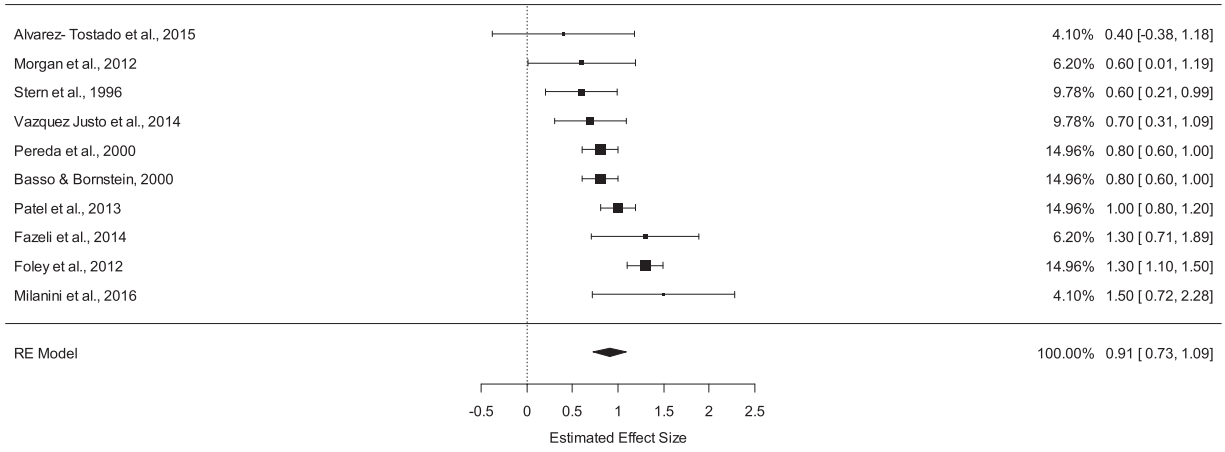

Figure 2. Forest plot showing the results of random-effects meta-analysis.

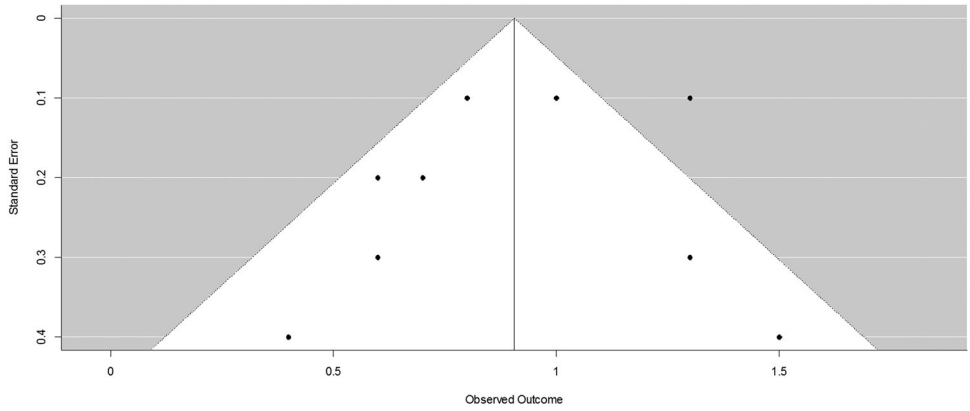

Figure 3. Funnel plot of estimated effect size versus standard error.

Although we found a strong association between cognitive reserve and cognitive ability in HIV, risk of bias and heterogeneity due to numerous factors in the reviewed studies should not be overlooked. The methodological quality of the studies included in this review contributed to the heterogeneity as all studies had a strong likelihood of non-responder bias and some risk of selection bias (O'Connor & Sargeant, 2014; Tanaka & Kawakami, 2015). Although some authors ensured recruitment of participants from a variety of sources, they did not justify whether their sample was representative of the target population. Indicating the rate of non-participation and the reasons for refusal in future studies would facilitate interpretation of the results (Sedgwick, 2015). All reviewed studies took confounding into consideration. For studies where both unadjusted and adjusted parameters were available (e.g., Fazeli et al., 2014; Vázquez-Justo et al., 2014), the results were similar, suggesting adjustment did not have a large effect.

Diverse parameters of effect size were reported across studies, which was challenging for quantitative synthesis. To harmonize these parameters, different statistical approaches had to be employed to derive a common metric of effect size (Thalheimer & Cook, 2002). It is recommended that researchers routinely report statistical parameters which can contribute to a meta-analysis. In some situations, we had to estimate the parameters required to compute effect size or its precision from the information available. For Basso and Bornstein (2000), the sample size was estimated based upon the distribution of data. For Milanini et al. (2016), log odds ratios were presented by increments of one unit on the cognitive reserve measure. For generating compatibility with other studies, the regression coefficient representing one unit difference was standardized to represent a clinically meaningful difference in cognitive reserve based on values presented for distinguishing high versus low of cognitive reserve (Milanini et al., 2016).

In addition to methodological reasons for the high heterogeneity observed across the studies, there were also clinical and measurement differences (Zhao, 2013; Gagnier, Moher, Boon, Beyene, & Bombardier, 2012). Heterogeneity could also have arisen from the differences concerning the recruited participants (inclusion in age, gender, years of diagnosis since HIV, disease severity, treatment regimen, study location), operational definitions of cognitive reserve and cognitive ability based on differences in the neuropsychological test batteries used. For example, Basso and Bornstein (2000) used extensive testing of executive functioning and did not test other cognitive domains (e.g., memory, processing speed), unlike others who used a wider spectrum of cognitive tests. Although the definitions of cognitive reserve seem to be consistent across the majority of studies included in this review (perhaps due to restricted eligibility criteria), dissimilarities were found in how proxy measures were combined when operationalizing cognitive reserve. Verbal IQ, education and occupation were relatively frequently employed proxies. It is also important to underscore that there is some degree of correlation between the measures used to quantify cognitive reserve (such as vocabulary and reading ability) and the measures used to quantify cognitive ability (D'Aniello, Castelnuovo, & Scarpina, 2015; Shakeel & Goghari, 2017) leading to a concern that relationships under study could be circular, perhaps inflating the degree of association. Until a consensus is reached on the operational definition of cognitive reserve, the diversity arising from the use of various proxies and scoring methods will persist.

Cognitive reserve is an important concept in the context of rehabilitation because it could be a prognostic construct and also a target of intervention (Vance, 2013b; Vance et al., 2016 Vance, Fazeli, Grant, Slater, & Raper, 2013a). Relationships between and among the

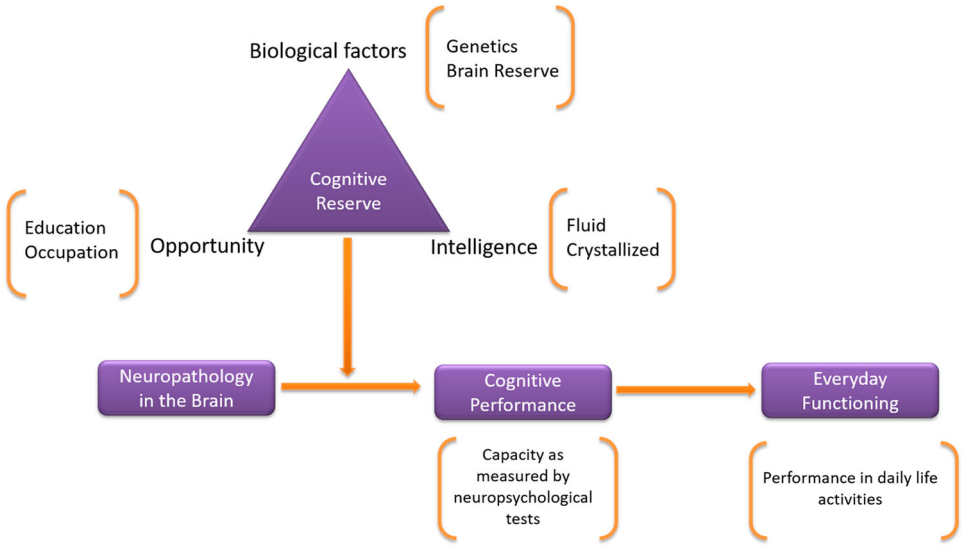

Figure 4. Hypothesized relationship between cognitive reserve and neuropathology.

various factors that have been linked to cognitive reserve and their consequences to cognitive impairment and beyond in Figure 4. Cognitive reserve is shown at the center of a triangle formed by biological factors, opportunity, and intelligence (measured by IQ). Under biological factors are genetics (Vázquez-Justo et al., 2014) and brain reserve, usually assessed through brain imaging (Christensen et al., 2007). The term "opportunity" was chosen to represent the typical contributors to cognitive reserve such as education and occupation to reinforce that these are not necessarily solely characteristics of the person, but also influenced by the social, political, and economic environment of the person. IQ has been categorized into fluid and crystallized intelligence. Cognitive reserve is hypothesized to mediate the negative effects of HIV neuropathology on cognition, preserving neuropsychological and real-life function despite brain injury.

Limitations

This meta-analysis accrued data from cross-sectional studies, so causation cannot be established between cognitive reserve and cognitive ability. Based on the quality appraisal, sensitivity analysis was deemed futile as there was little variation across studies in risk of bias. As recommended by the Cochrane Consumers and Communication Group (Ryan & Cochrane Consumers and Communication Review Group, 2016), a meta-regression should be attempted when there are at least 10 studies. Our attempt to explore heterogeneity was hindered by the fact that the articles were lacking in a common set of variables which could be used as moderators or explanatory variables. For example, not all studies employed the same HIV disease indices (e.g., nadir CD4).

As our meta-analysis was restricted to the articles published in English, this could have introduced language bias. However, evidence has shown that excluding non-English publications generally has modest impact on summary estimates (Jüni, Holenstein, Sterne, Bartlett, & Egger, 2002). A major limitation of this work arises from the fact that the included studies presented a variety of effect parameters which had to be transformed to obtain a common metric of effect size. The underlying statistical assumptions for these transformations were not always verifiable.

Conclusion

Although more research is required in this area, the relationship between cognitive reserve and cognitive ability suggests that people with HIV who have low cognitive reserve might be more prone to neurocognitive difficulties and this might need consideration in evaluation and treatment planning. The findings of this review should be interpreted with caution as the literature in this area poses challenges due to methodological heterogeneity. The limitations in the studies included in this review point out an opportunity for scientists to create a harmonized set of parameters for studying the association between cognitive reserve and neurocognitive performance in HIV that could be used in future studies of this important topic.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Chapter 4: Integration of Manuscripts I & II

Research Objective of Manuscript I

To estimate, based on published studies, the strength of the association between cognitive reserve and cognitive performance in individuals with HIV.

Research Objective of Manuscript II

To develop an index of cognitive reserve for people with HIV based on combining multiple indicators of cognitively stimulating life-time experiences into a single value.

Cognitive reserve is a promising concept as it proposes that clinical manifestations of brain pathology could be delayed with participation in cognitively stimulating life experiences. Manuscript I presented a comprehensive review of the literature on the association between cognitive reserve and cognitive performance in HIV. Based on the evidence available from the cross-sectional studies, it was concluded that there is a there is a correlation of 0.4 between the two. Additionally, it was observed education, IQ and occupation were most commonly used indicators to operationalize cognitive reserve in the neuroHIV literature. However, these were often inconsistently combined.

Although the indices of cognitive reserve exist in the literature other than HIV (Nucci et al., 2011; Valenzuela & Sachdev, 2006), most do not capture the unique influence of indicators of cognitive reserve. It would be valuable to produce an index that has been built based upon the differential contributions of cognitive activities in HIV. Focusing on the specific indicators that were captured in the Positive Brain Health Now (+BHN) database, the subsequent manuscript in this thesis documents the development of an index of cognitive reserve. Additionally, it will cover the validation of the index based on its association with cognitive ability and the measures of everyday functioning.

Chapter 5: Manuscript II

Development and Validation of a Cognitive Reserve Index in HIV (CRI-HIV)

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Abstract

Introduction: In the neuroHIV literature, cognitive reserve has most often been operationalized using socio-behavioural indicators mainly including education, occupation and IQ. However, the effects of other cognitively stimulating activities (e.g., social and intellectual activities), that might be more amenable to intervention, have not been given much attention. The purpose of this study was to develop an index of cognitive reserve in people with HIV based on combining multiple indicators of cognitively stimulating lifetime experiences into a single value. Also, this study contributed evidence for the convergent validity of Cognitive Reserve Index in HIV (CRI-HIV).

Methods: The dataset for this study was obtained from the Positive Brain Health Now cohort (N=856). Potential cognitive reserve indicators captured in this cohort included education, occupation, engagement in other cognitively stimulating activities, number of languages spoken, and social support. Cognitive ability was measured with the Brief Cognitive Ability Measure (B-CAM). The index was formulated using beta-weights derived from univariate logistic regression analysis for each indicator. Pearson correlation coefficients with 95% confidence intervals (CI) were estimated between the CRI-HIV score and B-CAM at follow-up and measures of everyday functioning (Perceived Deficits Questionnaire; PDQ, and Stanford Presenteeism Scale; SPS) both at baseline and follow-up.

Results: High school education to university education, professional/executive work and other cognitively stimulating activities such as visual arts (any level of engagement), professional/amateur music, games (any level of engagement), travel outside North America, and professional sports predicted high cognitive ability in HIV. Therefore, these were included in the index. The CRI-HIV was moderately associated with B-CAM at follow up (r = 0.3; 95% CI: 0.23

to 0.38). As expected, it had a modest association with measures of everyday functioning.

Conclusion: This work contributed evidence towards the relative benefit, to people with HIV, of engaging in specific cognitively stimulating life experiences.

Background

Despite effective antiretroviral treatment, as many as 30-50% of individuals with HIV infection experience some degree of cognitive impairment, which may adversely impact instrumental activities of daily living [1, 2] including medication adherence,[3, 4] driving,[5, 6] employment, and health-related quality of life[7, 8] and contribute to accelerated mortality.[9]

Could people living with HIV somehow protect themselves from cognitive impairment? Cognitive reserve is conceived of as a potential buffer against the impact of brain pathology on cognitive performance. Cognitive reserve, built up through cognitively enriching experiences over the lifespan, is thought to explain, at least in part, the disparity between a given degree of brain pathology and its clinical manifestations. [10] Although mainly studied in relation to aging and Alzheimer's disease, cognitive reserve has been proposed as relevant in HIV.[11] It is hypothesized to mediate the relationship between neuropathology and cognitive performance,[12-15] rather than having a strong direct effect on cognition *per se*. In turn, cognitive performance affects outcomes related to functioning in everyday life.[6]

While in the neuroHIV literature cognitive reserve has most commonly been operationalized using conventional indicators: education, occupation and IQ,[13] there is some evidence in the aging literature that physical, social, and intellectual activities often done as part of leisure and recreation may also contribute to cognitive reserve.[10, 14, 16, 17] These are of particular interest, as they are more amenable to change in adulthood, offering the potential for intervention.

A broader view of indicators of cognitive reserve may be relevant, but there are measurement and statistical challenges in quantifying cognitive reserve using multiple indicators. [18] Combining all the potential indicators, i.e. education, occupation, IQ, and leisure activities, into one quantity, is not straightforward. Previous work has used a mix of principal component analysis, item response

theory, regression, and standardization of subscales scores to sum the items to derive indices. [19-22] An alternative method involves application of weights based on the influence that each potential indicator has on a relevant outcome. Impact weights have been used to generate indices of cardiovascular and stroke risk. [23, 24] Likewise, comorbidity indices have been developed based on the impact on mortality and length of hospital stay,[25] and recovery from stroke.[26] This approach has been scarcely used in developing an index of cognitive reserve. Here, for the first time, we apply this approach to develop an index of cognitive reserve in HIV.

The primary aim of this study is to develop an index of cognitive reserve for people living with HIV based on combining multiple indicators of cognitively stimulating lifetime experiences into a single value. A secondary aim is to contribute evidence for the convergent validity of Cognitive Reserve Index in HIV (CRI-HIV).

The hypothesis is that the CRI-HIV will correlate moderately with cognitive performance and weakly with everyday function, which is more directly affected by cognitive performance rather than cognitive reserve.

Methods

The data for this study were acquired from the Positive Brain Health Now (+BHN) cohort,[27] comprised of 856 HIV-positive participants recruited from 5 clinics in 4 Canadian cities: Montreal, Toronto, Hamilton, and Vancouver. The eligibility criteria for this cohort are presented in Supplementary Table 1.

A computerized battery testing executive functions, memory and attention with the following tasks: Corsi block task (forward and backward), mini Trail-Making Test B, Eriksen flanker task, phonemic fluency and recall of a list of 8 words was administered at study enrollment and every 9 months over 27 months of follow-up.[28, 29] The primary outcome measure was overall cognitive

ability, estimated from test performance (Brief Cognitive Ability Measure B-CAM©) using a Rasch-based approach. [29] The B-CAM score was transformed into a binary variable (high/low) with individuals scoring at or above the 75th percentile ($\geq$ 23) considered to have high cognitive ability. Socio-demographic and clinical variables including years since HIV diagnosis, nadir CD4 cell count, and percentage of participants with nadir CD4 count <200 cells/μL were obtained from +BHN dataset. All participants were on anti-retroviral therapy.

Self-reported cognitive difficulties and work productivity were ascertained using the Perceived Deficits Questionnaire (PDQ) [30] and Stanford Presenteeism Scale (SPS), [31] both deemed to be indicators of everyday functioning. The PDQ is composed of 20 items and asks participants to report on their cognitive functioning within the previous 4 weeks. It yields a total score ranging from 0 to 80, with a higher score indicating the presence of more cognitive difficulties. A score of 40 on the PDQ indicates cognitive impairment. The SPS assesses work productivity among employed individuals, with higher scores indicating better work productivity; it has a total score of 50.

Indicators of cognitive reserve measured in the +BHN dataset included: education, occupation, social support, number of languages spoken and engagement in other cognitively engaging activities. Education was categorized into primary, high school, collegiate diploma programs, bachelor degree, or graduate degrees including medicine and law. Work was classified as professional, administrative or clerical. The other cognitively engaging experiences included visual arts (such as painting, drawing, photography), music, performance/literary arts, sports, travel and games. The level of engagement ranged from professional, amateur, personal enjoyment to none in the first four activities.

For travelling, the lowest level of engagement was indicated by travel within province and the

highest level of engagement was indicated by travel to more than 2 continents outside North America. For games, level of engagement was classified into four categories: competitive games, complex games (e.g., virtual reality), simple card/board games or none. Social support was elicited with the first three items of the Older Americans Resources and Services Social Resources Scale (OARS; Supplementary Table 2.).[32] A list of the indicators captured in +BHN cohort has been provided in the Appendices.

Statistical Analysis

Polychoric correlations were computed for the association between all the indicators of cognitive reserve (as these were ordinal variables). Logistic regression was used to identify the extent to which each indicator was associated with the probability of having a high B-CAM (score ≥ 23). All indicators were categorical and the reference category was the lowest level for each. Regression parameters, odds ratios (OR) and 95% confidence intervals (CI) were calculated for each indicator. The lowest regression coefficient (β) associated with an OR that excluded the null value (1.0) was taken as the cut-off for inclusion of that category in the index. This corresponded to a β of 0.5 and an OR of 1.7. All variables with at least one category with β≥ 0.5 were included whether or not their associated 95% CI excluded 1.0. Non-different levels in each categorical indicator were combined and the models were re-evaluated. Weights were assigned to the levels of each indicator by multiplying the regression coefficient (β) by 10. A weighted index (CRI-HIV) was derived by summing the βx10, noting that βs are additive while the ORs are not. These methods are illustrated in Figure 1.

To evaluate the convergent validity of the index, Pearson correlation coefficients were estimated between the CRI-HIV score and B-CAM at follow-up, and with PDQ and SPS both at baseline and follow-up. The corresponding 95% CI were presented for each. Based on widely adopted

benchmarks, correlations of 0.1, 0.3, and 0.5 were considered as small, medium, and large, respectively. [33] All statistical analyses were carried out using SAS version 9.4 for Windows (SAS Institute, 100 SAS Campus Dr, Cary, NC, USA).

Results

Table 1 shows the characteristics of the full sample at baseline and at the last follow-up visit. As there was attrition over time, also shown are the values at baseline for those with follow-up. At baseline, the mean age of the entry sample was 53.0 years (SD: 8.3) and there were more men (84%) than women (16%). Among those with follow-up, the mean age was very similar (53.4 years; SD: 8.3). This similarity between values for the entry sample and those with follow-up was observed for the other measures. The mean time between baseline and follow-up assessments was 25.9 months (SD = 7.21). All participants in the +BHN cohort were taking combined antiretroviral therapy.

Correlation between all indicators of cognitive reserve was low with the exception of education and work (polychoric $r = 0.5$), music and performance arts (polychoric $r = 0.4$), and visual arts and performance arts (polychoric $r = 0.4$). All indicators were retained based on these correlations. Figure 1 shows the methods for creating the scoring algorithm to derive CRI-HIV score based on those variables with at least one category meeting our criterion for inclusion (OR: 1.7; β: 0.5). Column 1 presents the indicator and column 2 gives the categories within each indicator.

Column 3 presents the frequency distribution across indicator-categories. For education, the modal category was college education (34%) and only 10% of the sample had a masters or doctoral degree. Across the other cognitively engaging activities, the most frequent level of engagement was for “personal enjoyment”. Higher levels of engagement were rare: visual arts,

8%; sports, 9%; performance arts, 13%; games, 14%; and music, 26%. Travel outside of North America was common (56%). Only 39 % of the sample were monolingual but no category of multilingualism met our criterion for inclusion (OR: 1.7; β: 0.5). This was also true for variables relating to social network.

Column 4 presents the βs for each of the categories of the included indicator variables and column 5 gives ORs. The categories with green highlighting are those fulfilling the criteria for inclusion, those with orange highlighting did not and were combined as shown in column 6. For example, for work, as service/clerical and highly skilled or administrative jobs did not differ, they were combined and served as the referent category for the professional/executive level. For visual arts, each category was unique. For music, sports, and travel, only one category was retained; for games two categories were retained; and for performance arts, none of the categories were retained. The regression coefficients, ORs and corresponding 95% CI have also been presented in Supplementary Table 3.

Column 7 shows the weights assigned to these specific category-indicators. Masters and doctoral level of education received the highest points (15) whereas bachelor's degree, college level and high school received 14, 10 and 6 points, respectively. The maximum possible score of the index is 109. Figure 2 shows that the distribution of the CRI-HIV score was approximately normal. In this sample, the highest achieved score was 52. The mean score was 23.2 (median: 24; SD: 9.0).

Table 2 shows correlation coefficients between the CRI-HIV score and B-CAM and everyday functioning, respectively. The CRI-HIV score and B-CAM at follow-up were moderately correlated (r = 0.3; 95% CI: 0.23 to 0.38). Correlation between the CRI-HIV and PDQ at baseline and PDQ at follow-up was -0.15 (95% CI: -0.21 to -0.08) and -0.16 (95% CI: -0.23 to -0.08), respectively. Correlation between the CRI-HIV score and SPS at baseline and SPS at follow-up

was 0.15 (95% CI: 0.06 to 0.23) and 0.13 (95% CI: 0.03 to 0.21), respectively.

Discussion

In this study, various contributors of cognitive reserve were combined into an index of cognitive reserve (CRI-HIV) based on their impact on a measure of cognitive performance in older people living with HIV. As hypothesized, this index was shown to have a moderate association ($r = 0.3$) with cognitive performance in this sample. As expected, the CRI-HIV index was weakly correlated with the follow-up measures of everyday functioning, but the correlations were in the expected direction, with more reported cognitive difficulties and less work productivity (see Table 2).

The CRI-HIV was based on a formative measurement model as various indicators (such as education, occupation and lifestyle pursuits) form the construct of cognitive reserve. The direction of the relationship is from the items to the construct in a formative model. This is in contrast to reflective models where the construct is a feature of the person and is reflected in many different factors, measured and unmeasured (Edwards & Bagozzi, 2000).

This index can be applied in research settings to adjust for the effect of multiple indicators such as education, occupation and other cognitively engaging pursuits in a parsimonious manner. This might be particularly useful in clinical trials, e.g. of cognitive training or rehabilitation programs, as participants may respond to interventions based on their cognitive reserve. The index also avoids the statistical challenges (interpretation, collinearity, reduced power) associated with the common practice of accounting for the effects of each indicator individually.[34, 35] Moreover, the index may aid the clinical interpretation of the scores from neuropsychological tests.

There is a consensus that leisure or recreational activities are important in cognitive reserve, in addition to education and occupation in the non-HIV literature. [15, 16, 36-38] One of the unique features of this study is the demonstration of the relative benefit of engaging in specific cognitively stimulating life experiences for those living with HIV. A recent white paper on cognitive reserve highlights the need for such measures to improve upon the current summary approach.[10] To our knowledge, the present study was the first attempt to tease out the relative contributions of specific life experiences of people with HIV on cognitive performance.

This study showed that cognitively stimulating activities such as visual arts (any level of engagement), professional/amateur music, games (any level of engagement), travel outside North America and professional sports predicted high cognitive ability in people with HIV. These were included in the index. Conceptually, cognitive reserve is believed to be a dynamic entity that can be enhanced through engagement in cognitively stimulating activities across the lifespan.[10] Our work suggests that those who did not have the opportunity to acquire a high level of education could benefit from recreational activities, especially visual arts and games.

Although extensive travel seems to have a cognitively nurturing effect based on our findings, it may not be a pragmatic option to boost reserve, given the expense involved. That said, the correlation between travel and other indicators of high socio-economic status (education and occupation) was only 0.3, considered weak under the assumption that they are part of the same latent construct.

A variety of cognitive reserve indices and questionnaires have been developed among diverse populations. [19-22] Overall, these measures vary in the type of cognitively engaging pursuits covered, their number, frequency and timeframe. The CRI-HIV is to date the only index based on a scoring algorithm which takes impact weights, of each contributing indicator, into

consideration to quantify cognitive reserve in HIV.

Employment status may fluctuate during the lifetime of an individual. [39] Therefore, participants in this study were asked to choose their level of engagement in a job based on their longest job instead of their current or last job. This study showed a relationship between the CRI-HIV and work productivity in HIV. Work productivity has not been extensively studied in HIV. Most studies focus on employment status and its relationship with neurocognitive abilities and everyday functioning among people living with HIV and have suggested that employment may be a way of preserving cognition. [8, 40] The present study found that higher cognitive reserve was associated with higher work productivity in people with HIV who were employed, although the effect size was small.

Social network was not incorporated into the CRI-HIV as the association between B-CAM and the social network variables available in this study was weak. Concordant with this finding, a 2018 meta-analysis (n= 30,037) also revealed a weak association between social network and measures of cognitive performance (r=0.072) [12] in healthy older adults.

Although bilingualism has been proposed to foster cognitive reserve, bi-or- plurilingualism did not contribute to the index in our sample. There are mixed findings from studies examining the relationship between bilingualism and cognitive reserve among people with Alzheimer's disease.[41] The disparity across studies could have arisen due to the differences in the paths to plurilingualism (voluntary learning versus necessity), sampling procedures and outcome measures used to investigate this area. [42]

It is important to underline that the evidence for the cognitive reserve hypothesis is mostly observational: causal evidence for its potential protective effect on cognition is needed. Clinical trials have shown that interventions e.g., a 12-week cognitive music training (N=35) [43], or a 14-

week “productive engagement” in learning digital photography alone or in combination with learning to quilt (N=259) [44] rendered benefits to specific cognitive processes (assessed using neuropsychological tests) among older adults.

Rigorous randomized controlled trials of the contributors to cognitive reserve are needed to strongly recommend interventions that can promote cognitive performance in HIV. While awaiting such evidence, it seems worthwhile to encourage participation in cognitively stimulating activities as these are unlikely to do harm.

Limitations

Our choice of indicators was limited to the ones available in the dataset. For example, engagement in learning activities post-formal education was not captured. Also, we did not have data on IQ available to include in the CRI- HIV, although it is traditionally considered in the mix of indicators of cognitive reserve. Cognitive reserve and IQ could be correlated but they also seem to be distinct concepts. Nucci and colleagues excluded IQ from their index of cognitive reserve and suggested that IQ relates to intellectual performance whereas cognitive reserve is based on an accumulation of resources acquired through a lifetime of cognitively engaging pursuits. [20] Other scales and questionnaires of cognitive reserve in non-HIV populations also do not include IQ. [19, 21, 22]

All the indicators of cognitive reserve could have been affected by recall, [45] mood and social desirability. Also, everyday functioning was captured using self-report measures, which can be inaccurate. [40] Proxy-reporting of cognitive difficulties was not done nor was work productivity employer-confirmed. Such data would involve additional ethics considerations and were beyond the scope of the cohort study. The B-CAM is a brief computerized assessment that includes tasks used in standard neuropsychological tests and has been developed using modern

psychometric techniques. However, it is not a full neuropsychological assessment.[28]

In this work, the criteria used for inclusion of indicators in the CRI-HIV, i.e., $\beta = 0.5$ and OR = 1.7, were data driven and not based on any precedent or theory. The threshold was chosen to allow every indicator to have the same criterion to enter the index regardless of the degree of statistical significance associated with the regression parameter. It is important to mention that the professional level of engagement in a specific role, education and occupation may vary across individuals. For instance, a seasoned university professor with extensive experience in teaching and research may have different level of engagement as compared to a junior professor. Such differences in engagement were not captured by the CRI-HIV and future studies should explore ways to do so.

We did not use adjusted β-weights because of the independent nature of the variables under study. No adjustments for the effect of all indicators were deemed necessary as an individual is unlikely to be engaged in all of them.

Conclusion

This study documented the development of an index of cognitive reserve in older people living with well-controlled HIV infection. The CRI-HIV was moderately correlated with cognitive ability measured at follow-up, and more modestly associated with measures of everyday functioning such as self-perceived cognitive deficits and work productivity. The latter are likely to be more strongly related to cognitive ability and have a multitude of predictors unrelated to cognitive reserve.

The index developed here might also apply to clinical groups other than people living with HIV; further work would be needed to test its generalizability. The index can serve as an efficient research tool to quantify and account for the effect of cognitive reserve. Lifestyle-modifying intervention strategies should integrate avenues for 'reserve-building' pursuits, especially for those who may not have had the opportunity to acquire extensive education or achieve high occupational

complexity. Such reserve-building strategies need to be tested in randomized trials, to provide the causal evidence that remains scarce in work on cognitive reserve.

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Table 1. Characteristics of the sample (N=856)

Characteristic	Baseline (N=856)	Baseline with follow- up	Follow-up (N=758)
Age (years)	53.0 (8.2)	53.35 (8.3)	55.4 (8.3)
Men / Women (n %)	722 (84%) / 134 (16%)	667 (85%) / 116 (15%)	667 (85%) / 116 (15%)
B-CAM	19.6 (4.7)	19.8 (4.7)	20.9 (4.4)
PDQ	34.1 (17.8)	33.4 (17.5)	32.5 (17.2)
SPS	39.7 (6.4)	40.4 (6.2)	39.9 (6.7)
Time between assessments (months)			25.9 (7.21)
Years with diagnosis	17 (7.8)		19.14 (8.0)
Nadir CD4 / % <200[a]	217.05 (169.15) / 51%		212.91 (163.4) / 52%

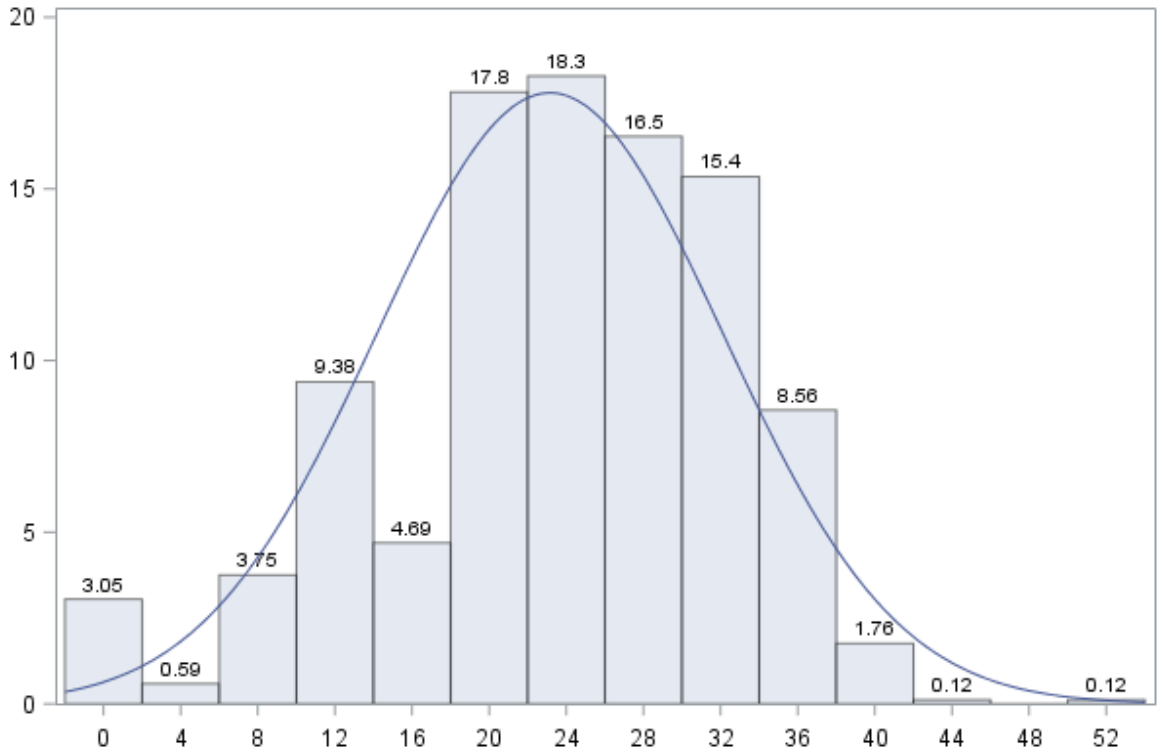
[a]CD4 Count <200 cells/μL

B-CAM = Brief-Cognitive Ability Measure; higher scores are better, PDQ = Perceived Deficits Questionnaire; ≥40 indicates cognitive impairment, and SPS = Stanford Presenteeism Scale; higher scores are better.

Indicator	Levels	n(%)	β >0.5	OR	Combinations	Weights
Education	Primary School	38 (5)	Referent		Referent	0
	High School	228 (28)	0.6439	1.90	0.6439	6
	CEGEP/College	284 (34)	1.0522	2.86	1.0522	11
	Bachelor degree	196 (24)	1.3576	3.89	1.3576	14
	Masters/PhD	82 (10)	1.5142	4.55	1.5142	15
Work	Service/Clerical	303 (37)	Referent		Referent	0
	Highly-skilled/Admin	339 (42)	0.3667	1.44		
	Professional/Executive	170 (21)	0.6429	1.90	0.439	4
Visual arts	None	219 (27)	Referent		Referent	0
	Personal enjoyment	529 (65)	0.6782	1.97	0.6782	7
	Amateur	48 (6)	0.8049	2.24	0.8049	8
	Professional	16 (2)	0.8815	2.41	0.8815	9
Music	None	146 (18)	Referent		Referent	0
	Personal enjoyment	456 (56)	0.2874	1.33		
	Amateur	123 (15)	0.8711	2.39	0.5888	6
	Professional	87 (11)	0.561	1.75		
Sports	None	309 (38)	Referent			
	Personal enjoyment	434 (54)	0.1315	1.14	Referent	0
	Amateur	61 (8)	0.0795	1.08		
	Professional	7 (1)	1.1987	3.32	1.1205	11
Travel	Within province	188 (23)	Referent		Referent	0
	Within North America	168 (21)	0.0878	1.09		
	1 continent other than NA	191 (24)	0.5793	1.78	0.5878	6
	2 continents other than NA	260 (32)	0.6663	1.95		
Games	None	291 (36)	Referent		Referent	0
	Simple card/board games	410 (50)	0.5394	1.71	0.5394	5
	Complex video games	88 (11)	0.8836	2.42	0.7325	7
	Competitive games	26 (3)	0.1031	1.11		
Performance Arts	None	352 (44)	Referent			
	Personal enjoyment	350 (43)	0.3497	1.42	Referent	0
	Amateur	62 (8)	-0.0662	0.94		
	Professional	43 (5)	0.5148	1.67	0.3612	0

Figure 1. Development of Cognitive Reserve Index in HIV (CRI-HIV)

(β = Regression coefficient; OR= Odds ratio)



Weighted Index Score (Mean = 23.2; SD =9.0; Median = 24)

Figure 2. Distribution of cognitive reserve index score in HIV (CRI-HIV)

Table 2. Pearson product-moment correlations between various measures employed in this study

	CRI-HIV Score	B-CAM (follow-up)	PDQ (baseline)	PDQ (follow-up)	SPS (baseline)	SPS (follow-up)
CRI-HIV Score		0.30[a] [0.23 to 0.38][b]	-0.15 [-0.21 to 0.08]	-0.16 [-0.23 to -0.08]	0.15 [0.06 to 0.23]	0.13 [0.03 to 0.21]
B-CAM (follow-up)			-0.36 [-0.42 to -0.29]	-0.43 [-0.49 to -0.36]	0.30 [0.21 to 0.38]	0.36 [0.27 to 0.44]
PDQ (baseline)				0.76 [0.72 to 0.78]	-0.61 [-0.66 to -0.55]	-0.50 [-0.57 to -0.43]
PDQ (follow-up)					-0.47 [-0.53 to -0.39]	-0.62 [-0.67 to -0.56]
SPS (baseline)						0.51 [0.43 to 0.58]
SPS (follow-up)						

[a]Pearson correlation

[b]95% CI

CRI-HIV = Cognitive Reserve Index in HIV; B-CAM = Brief-Cognitive Ability Measure; higher scores are better,
PDQ = Perceived Deficits Questionnaire; ≥40 indicates cognitive impairment, and SPS = Stanford Presenteeism Scale; higher scores are better.

Supplementary Table 1. Eligibility Criteria for +BHN Cohort; N=856 [27]

Inclusion Criteria
Age ≥35, HIV+ men and women for at least 1 year, able to communicate adequately in either French or English, and able to give written informed consent. Also, individuals with current or past major depressive disorder were eligible.
Exclusion Criteria
Thus, exclusion criteria include dementia based on Memorial Sloan-Kettering (MSK) dementia severity scale rating of Stage 3 or more on the cognitive component, treating physician's concern about capacity to consent, life expectancy of <3 years or other personal factor limiting the ability to participate in follow-up, non-HIV-related neurological disorder likely to affect cognition, known active CNS opportunistic infection or hepatitis C requiring interferon-based treatment during the follow-up period, psychotic disorder, or current substance use disorder or severe substance use disorder within the past 12 months.

Supplementary Table 2. Frequency distribution of levels in each indicator of cognitive reserve (N=856)

Indicator	N	%
Education		
Primary school	38	5
High school	228	28
CEGEP/College	284	34
Bachelors	196	24
Masters/PhD degree	82	10
Work		
Clerical	303	37
Highly-skilled	339	42
Professional/Executive	170	21
[a]Number of languages spoken		
1	300	39
2	307	40
3	126	16
4	34	4
Visual Arts		
None	219	27
Personal enjoyment	529	65
Amateur	48	6
Professional	16	2
Music		
None	146	18
Personal enjoyment	456	56
Amateur	123	15
Professional	87	11
Performance/Literary Arts		
None	352	44

Personal enjoyment	350	43
Amateur	62	8
Professional	43	5
Sports		
None	309	38
Personal enjoyment	434	54
Amateur	61	8
Professional	7	1
Travel		
Within province	188	23
Within North America (NA)	168	21
1 continent other than NA	191	24
2 continents other than NA	260	32
Games		
None	291	36
Simple card/board games	410	50
Complex games	88	11
Competitive games	26	3
[b]OARS item 1		
None	413	53
1-2	193	25
3-4	142	18
5 or more	25	3
[c]OARS item 2		
< Once a week	374	48
Once a week	281	36
Almost everyday	82	11
1 or more times a day	35	11
[d]OARS item 3		
< Once a week	76	10
Once a week	251	33
Almost everyday	270	35

1 or more times a day	173	22

[a]All levels not presented so percentages do not add up to 100; [b]How many people do you know well enough to visit within their homes? [c]About how many times in the past week did you talk to someone (friends, relatives or others) on the telephone, or by text message, or internet? [d]How many times during the past week did you spend some time with someone who does not live with you, that is you went to see them or they came to visit you or you went out to do things together?

OARS = Older Americans Resources and Services (Social Resources Scale)

Supplementary Table 3. Logistic regression parameters and weights assigned for each indicator which contributed to the CRI-HIV

Indicator	β	SE	OR	95% CI	Weight assigned
Education					
High school	0.6439	0.63	1.9	0.55 – 6.55	6
CEGEP/College	1.0522	0.62	2.9	0.85 – 9.64	11
Bachelors	1.4050	0.62	4.1	1.21 – 13.6	14
Masters/PhD	1.5142	0.63	4.5	1.42 – 11.4	15
Work					
Professional	0.4390	0.20	1.6	1.04 – 2.30	4
Visual arts					
Personal enjoyment	0.6782	0.28	1.9	1.13 – 3.43	7
Amateur	0.8049	0.33	2.2	1.15 – 4.32	8
Professional	0.8815	0.35	2.4	1.19 – 4.88	9
Music					
Amateur/Professional	0.5888	0.28	1.8	1.02 – 3.17	6
Sports					
Professional	1.1205	0.76	3.1	0.67 – 13.8	11
Travel					
More than one continent other than NA	0.5878	0.18	1.8	1.25 – 2.58	6
Games					
Simple card/board games	0.5394	0.20	1.7	1.14 – 2.57	5
Competitive/Complex games	0.7325	0.27	2.1	1.21 – 3.55	7
Total weighted index score					109

β = Regression coefficient; SE = Standard error; OR = Odds ratio; CI: Confidence intervals; CRI-HIV = Cognitive Reserve Index in HIV

Chapter 6: Integration of Manuscript II and III

Research Objective of Manuscript II

To develop an index of cognitive reserve for people with HIV based on combining multiple indicators of cognitively stimulating lifetime experiences into a single value.

Research Objectives of Manuscript III

(i) To estimate the feasibility of a 12-week combined aerobic and resistance exercise program in individuals with HIV; and (ii) to estimate the extent to which participants changed cognitive ability, physical performance, and other brain health outcomes (self-reported cognitive deficits, anxiety/depression, fatigue and motivation) after 12 weeks of engagement with the structured exercise program.

The concept of cognitive reserve could be a useful concept for intervention research. As the impact of combined anti-retroviral therapy (c-ART) on the brain in HIV is not entirely positive, the therapeutic benefit of commonly undertaken leisure activities including physical activities that are generally safe, non-invasive, and cost-effective need to be investigated. Also, physical activity has been viewed as a contributor of cognitive reserve. The focal point of the subsequent manuscript is to estimate the feasibility and potential of efficacy of a 12-week combined aerobic and resistance exercise program on measured cognitive performance in people with HIV. As brain health is a multi-factorial construct, the extent of change on anxiety/depression, fatigue, motivation, and self-perceived cognition will also be investigated.

Chapter 7: Manuscript III

Feasibility and potential for efficacy of a structured exercise programme in improving cognitive performance in HIV

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Abstract

Background: Although exercise has been shown to have an impact on cardiometabolic and body composition outcomes in people with HIV, its effect on cognitive ability remains understudied. We designed a pre-post study to estimate the feasibility conducting a 12-week combined aerobic and resistance training program, where feasibility is of both the process and the potential for change in cognition and other brain health outcomes.

Methods: This feasibility study was part of a larger HIV project (Mayo et al., 2016a) based on a cohort multiple randomized controlled design that resulted in three groups: exercise intervention group; comparison group and refusers. Adults with sedentary lifestyle, ≥ 35 with HIV diagnosis for at least 1 year, without dementia and cardiovascular co-morbidities were eligible. The exercise program consisted of high-intensity interval training and resistance exercises 3 days/week. Specific feasibility outcomes were evaluated. Cognitive ability was measured by Brief Cognitive Ability Measure (B-CAM) in all three groups. Standardized tests of physical performance were carried out in the exercise group. Specific measures of brain health included Perceived Deficits Questionnaire (PDQ), SF-36 Mental Health Index (MHI), Vitality subscale of SF-36 and motivation. Responder status and reliable change was computed for B-CAM. Effect size and 95% confidence intervals were estimated for all physical performance measures.

Results: Recruitment process was quite laborious although adherence and acceptability outcomes were good. There was no change on B-CAM post-training in the exercise group. All physical performance measures benefited from the exercise training (effect sizes: 0.4 to 1.5).

Conclusion: Although the 12-week exercise program improved physical capacity, it did not yield gains in cognitive ability in this feasibility study.

Introduction

The prognosis for people with HIV in the resource-rich settings is optimistic owing to the widespread availability and use of combined anti-retroviral therapy (cART). Remarkably, the post-cART era has added approximately 43.1 years to the life of an individual affected with HIV (Gueler et al., 2017). Despite the elimination of detectable virus, HIV-associated neurocognitive disorders (HAND) continue to escalate with these gains in life expectancy. Numerous factors including co-morbidities associated with aging, adverse impact of cART (e.g., neurotoxicity), and low penetrability of cART into the brain which can harbour virus have led to ever-growing concerns about cognitive deficits in people living with HIV (Ghosh et al., 2017; Chawla et al., 2018).

Exercise has been identified as one of the top three alternative and complementary therapies that hold promise for improving the outcome of people with HIV (Standish et al., 2001). A meta-analysis has reported benefits of different exercise types in improving immunologic, virologic, cardiopulmonary, metabolic, and musculoskeletal outcomes, in addition to health-related quality of life (HRQoL) in HIV (Nixon et al., 2010). The evidence supporting the association of physical activity and cognition in HIV comes substantially from cross- sectional studies (Ortega et al., 2015; Fazeli et al., 2015; Dufour et al., 2013). A clinical trial on HIV men reported a between-group difference of 14 points [95% confidence intervals (CI): 0.7 to 27.3] in the cognitive sub-scale of Medical Outcomes Study HIV Health Survey following a 6- month aerobic and resistance training program) (Fillipas et al., 2006).

A meta-analysis (Kelly et al., 2014) in healthy older adults found that resistance training versus stretching improved measures of verbal reasoning [standardized mean difference (SMD) = 3.16;

95% confidence intervals (CI): 1.07 to 5.24]. In mild cognitive impairment (MCI), a systematic review with 7 clinical trials concluded that exercise can yield positive influence on cognitive abilities, particularly in global cognition, executive function or attention in MCI (Ohman et al., 2015).

Exercise-mediated physiologic mechanisms underlying brain health include elevated neurotrophin levels, improved vascularization, facilitation of synaptogenesis, mediation of inflammation, and reduced disordered protein deposition (Kim-Sanchez et al., 2014). These mechanisms are still a matter of debate: one specific hypothesis is that regular, vigorous exercise reduces chronic inflammation (Michigan et al., 2011), whether directly or through better metabolic status, which in turn has positive effects on brain and cerebrovascular function. These mechanisms might be important in HIV, given that infection leads to chronic low-grade systemic inflammation on the one hand, and various factors contribute to higher rates of the metabolic syndrome and accelerated atherosclerosis on the other (Falutz, 2011).

It has been projected that 70% of individuals with HIV will be 50 or older by the year 2020 in the US (United States Senate Special Committee on Aging, 2013) putting them in the age range where cognitive impairment would develop even in the absence of HIV. Therefore, this topic is both important and timely. In addition, exercise is an inexpensive intervention with widespread benefits to vascular and musculoskeletal health and few harms. Evidence for benefit to brain health and cognition in particular would likely encourage adoption of exercise by people with HIV.

A feasibility study was conducted with the following objectives:

a) to estimate the feasibility of a 12-week combined aerobic and resistance exercise program in individuals with HIV; and b) to estimate the extent to which participants changed cognitive

ability, physical performance, and other brain health outcomes (self-reported cognitive deficits, anxiety/depression, fatigue and motivation) after 12 weeks of engagement with the structured exercise program.

Methods

Study Design

A single arm, pre-post, feasibility study was conducted within a larger, ongoing, project [Positive Brain Health Now Cohort (+BHN); Mayo et al., 2016a] which is a cohort multiple randomized controlled trial (cmRCT) (Relton et al., 2010). This design, when operationalized for a single-arm (here of an exercise intervention), yielded three groups: (i) the intervention group, comprising all those approached and who agreed to enter; (ii) the refusers, comprising all those approached who declined entry; and (iii) a comparison group, comprising eligible participants who were not approached, and hence were not given the opportunity to accept or decline. The feasibility study was informed by the Consolidated Standards of Reporting Trials (CONSORT) guidelines for pilot and feasibility studies (Elridge et al., 2016). It was registered at clinicaltrials.gov (ID: NCT03053817). The ethics approval was obtained from the McGill University Health Centre (MUHC) and from the research ethics review committee at the Université du Québec à Montréal (UQAM).

Eligibility Criteria

The eligibility criteria for the +BHN cohort have been described previously (Mayo et al., 2016a). Briefly, the target population was people aged ≥35 years, HIV+ for at least 1 year, and able to communicate adequately in either French or English. Excluded were people who had dementia or had non-HIV-related neurological disorder, active CNS opportunistic infection, known psychotic

disorder, substance dependence or abuse within the past 12 months or life expectancy of <3 years as judged by the treating physician.

Specific Selection Criteria for Exercise Intervention

The exercise intervention targeted participants recruited in Montreal who identified at cohort entry they were interested in being approached for different trials if they were eligible. To be included, participants had to identify that they were mostly sedentary by reporting that they performed moderate level physical activity of 30 minutes duration less than twice a week or have limitations in performing vigorous activities, walking a kilometer, or climbing stairs. Excluded were people with a contraindication for exercise from cardiovascular or musculoskeletal co-morbidity as gathered from the medical history and from the Physical Activities Readiness Questionnaire (PAR-Q) (Thomas et al., 1992). Individuals answering yes to any of the PAR-Q items except taking medication (item 6) required clearance from their physician to be included.

Intervention

The 12-week exercise intervention was supervised and comprised: (i) aerobic exercise designed to increase physical fitness and cardiovascular health and (ii) resistance training to improve muscle strength, endurance, and performance. Current recommendations suggest that exercise programs that combine resistance exercise with aerobic training yield optimal health benefits for people with HIV (Malita et al., 2005). The 45-minute exercise program was performed 3 times a week (on alternate days) at a research-based gym at UQAM.

High-intensity interval training (HIIT) (Billat, 2001) using elliptical machines was performed for 21 minutes including a three-minute warm-up and cool-down period [60% to 65% of maximum heart rate (MHR)]. The interval program lasted around 15 minutes with 30 second bursts of exercise at an intensity of 80-85% of the MHR (>17 on Borg Scale; Williams, 2017) followed by

1 minute and 30 seconds of active recovery. Resistance training was carried out with weight machines. It was done in 2 sets of 12 repetitions and lasted 24 minutes. Due to their role in functional activities, hamstrings, pectorals, quadriceps, and latissimus dorsi were specifically trained. The resistance was set at 80% of the one-repetition maximum (1RM).

To ensure progressive overload, resistance was enhanced when participants were able to perform more than 15 repetitions. For core stabilization, contralateral arm and leg raises were performed in quadruped position. The workout concluded with the stretching of major muscle groups. Two exercise therapists were present at all times during the training to ensure the safe delivery of the intervention and to encourage adherence to the exercise regimen.

Measurement Strategy

The measurement strategy for this study has been outlined in Table 1. Feasibility of the exercise intervention was estimated as follows.

Proportion of participants recruited was recorded. Adherence to the intervention schedule was estimated by the number of sessions attended out of the total 36 sessions. Good adherence was defined as completion of at least 29 (80%) of the prescribed sessions. Acceptability of the intervention was estimated based on the ratings of perceived enjoyment at the end of the intervention. The participants were asked how much they enjoyed the exercise program on a scale of from 0 (did not enjoy at all) to 10 (enjoyed a lot). Feedback was obtained from each participant at the end of the intervention with an open-ended format.

The primary efficacy potential outcome was the Brief Cognitive Ability Measure (B-CAM) (Brouillette et al., 2015). This was part of the measurement platform in the parent study (+BHN; Mayo et al., 2016a) and the value taken at the regular assessment prior to the exercise

intervention served as the baseline and the subsequent evaluation following the intervention served as the follow-up value. The visits were pre-planned to be 9 months apart.

B-CAM consists of the domains of executive function, memory, attention and language, as evaluated by the following tasks: Corsi block task (forward and backward), mini Trail-Making Test B, Eriksen flanker task, verbal (phonemic) fluency and recall of a list of 8 words. Higher scores are indicative of better cognitive ability (Brouillette et al., 2015). A clinically meaningful change on B-CAM is equivalent to ½ a standard deviation (SD) (Norman et al., 2004).

Brain health indicators (self-perceived cognition, depression/anxiety, fatigue and motivation) were also part of the platform and were measured at the same time points as the B-CAM. The intervention took place in a 3-month period between the two 9-month apart assessments.

Perceived Deficits Questionnaire (PDQ) was used to reflect every day cognitive challenges as reported by the participants themselves. The PDQ consists of 20 items of self-perceived cognitive functioning over the previous 4 weeks (Sullivan et al., 1990). The response options range from 0 (never) to 5 (almost always). This measure taps into attention, retrospective memory, prospective memory, and planning and organization. It generates scores ranging from 0 to 80, with a score of 40 as a cut-off for cognitive impairment.

The brain health outcomes of fatigue and anxiety/depression were measured using the vitality subscale and mental health inventory (MHI), respectively from the Medical Outcomes Study Short Form 36 Health Survey (SF-36; a generic measure of health status) (Ware & Sherbourne, 1992). The subscale scores range from 0 to 100, with greater scores representing better health states.

Motivation was elicited using three questions: (i) Are you always looking for something to do? (ii) Are you interested in learning new things? (iii) Do you have plans and goals for the future? The response options ranged from not at all, some and a lot. It has a Rasch-derived score ranging from 0-42 and higher scores indicate better motivation. Socio-demographic characteristics of the three groups were obtained from the parent study (Mayo et al., 2016a).

Following measures were employed at baseline and after the 12-week intervention for the exercise group:

Modified Canadian Aerobic Fitness Test (mCAFT): This test has a high degree of reliability and validity for predicting exercise capacity (Weller et al., 1998). The procedure for this 3-minute multistage step test was standardized as documented in the Canadian Physical Activity, Fitness and Lifestyle Approach (CPAFLA) manual. The participants performed a series of stepping sequences with a predetermined musical cadence selected according to their age and gender (Weller et al., 1993; Weller et al., 1994; Jette et al., 1976). Participants were expected to complete all the stages required to achieve 85% of their age-predicted maximum heart rate. The maximal oxygen uptake (VO_2max) was predicted using this equation (Weller et al., 1993):

17.2 + (1.29 x oxygen cost at the final stage) - (0.09 x weight in kg) - (0.18 x age in years)

Six-Minute Walk Test (6-MWT): Functional capacity was determined with the 6MWT. The protocol was standardized as per American Thoracic Society guidelines (2016). The participants were instructed to walk at their own pace in an enclosed, flat 30-m-long track for six minutes.

They were allowed to stop if there were any symptoms of dyspnea or leg pain. The total distance covered at each minute and at the end was recorded. This test is reported to have high reliability and moderate validity (Finch et al., 2002).

Partial Curl-ups and Push-ups: These tests of muscle endurance were performed as outlined in the CPAFLA manual. The participants were instructed to do the maximum possible number of curl-ups at a rate of 25 per minute for 1 minute. In harmony with the cadence set by a metronome, upper spine was curled up until the middle finger-tips touched a 10-cm mark on the gym mat followed by slow return to the mat. During push-ups, participants were instructed to execute as many consecutive push-ups without any time constraints. The test was discontinued when the participants were seen to strain or used compensatory movements.

Grip Strength: Using Jamar dynamometer, 3 alternate trials for each hand were performed as stipulated in the CPAFLA manual. The best result of three trials for both the left and right hand was recorded, in kilograms (kg). Grip strength has an outstanding reliability (Bohannon & Schaubert, 2005) with a measurement error of around 2 kilograms (Schreuders et al., 2003).

Gait Speed: Both comfortable and fast gait speed were measured using instrumented walkaway system (GAITRite®. Initially, participants walked comfortably on a 4-metre track in a straight line, with an additional 2 metres at the beginning and the end to allow acceleration and deceleration. The time taken (in seconds) to complete the 4 metres was monitored. This was followed by 4-metre walk at a fast pace.

Dual-task gait speed: Participants were instructed to name as many fruits as they could while concurrently walking on a 4-metre track in a straight line at a comfortable pace (Plummer & Iyigun et al., 2018). To avoid rehearsal, instructions for the specific cognitive task were only

made when the beginning of 4-metre line was approached. The time taken to reach the finishing mark was recorded in seconds.

Verbal Fluency: Category fluency was measured by instructing the participants to produce as many unique words as possible (in either French or English) within a specific category (i.e., animals) in 1 minute in seated position (Shao et al., 2014). The number of unique correct words determined scores for each participant. Repeated words were only scored once (Lezak et al., 2004). Verbal fluency tasks have a well-documented validity for verbal ability and executive control (Shao et al., 2014).

Seated Leg Extension: Lower limb muscle power was measured with Nottingham Leg Extensor Power rig (Skelton, 2002). In seated position, participants were asked to push a pedal using the dominant leg which accelerated a flywheel (Bassey & Short, 1990). The leg was fully extended at the end of the push. The final angular velocity of the flywheel was used to compute the leg extension power. It is a considered as a safe and reliable method across all age groups (Bassey & Short, 1990).

Exercise Enjoyment: Participants were asked before the exercise training how much they enjoyed exercise in general on a scale of 0 (not at all) to 10 (a lot).

Sample Size and Analysis

Baseline characteristics of all three groups were summarized using descriptive statistics. Continuous variables were presented as mean±standard deviation. Categorical variables were reported as frequencies and percentages. Due to the nature of the study, no between-group comparisons were performed. This feasibility study was designed to identify the proportion of individuals with a cognitive response rather than calculating an average response for the primary

efficacy potential outcome, i.e., B-CAM. This is because a responder-status analysis provides more pertinent information both at a group level and at an individual level (Mayo et al., 2016b). With a simple responder-status analysis, it is possible to calculate the probability of achieving a certain responder proportion, which is instrumental for designing future trials.

With the assumption that the change on B-CAM is drawn from a binomial distribution, 30 subjects in the intervention group would allow detection of a positive response at $p<0.05$ if 7 or more persons respond, assuming an expected probability of response with no intervention of 10% (n=3) (stattrek.com binomial calculator). The extent to which the exercise participants changed after the 12-week intervention was estimated using a paired t-test for physical performance outcomes. Responsiveness was elicited in terms of standardized response mean (SRM) (Escobar et al., 2007; Terwee et al., 2003). The SRM was calculated as the mean change score divided by the standard deviation of changed scores. Corresponding 95% confidence intervals (CI) were presented. To account for measurement error and practice effects, reliable change index (RCI) was computed for selected outcomes based on the traditional methods (Jacobson & Truax, 1991; Chelune et al., 1993). Reliable change per group was defined by values larger than 1.645.

Results

A total of 27 participants completed the 12-week exercise training program. Figure 1 shows the flow of participants in the exercise program. The recruitment was slow and laborious as there was not much interest shown towards exercise among those who were contacted. Ninety-three participants refused the exercise training. Those who were eligible for the training outside Montreal were considered as altogether as an off- site comparison group (n=114).

Table 1 shows the characteristics of all three groups, i.e., exercise group (n=27); comparison group (n=114) and refusers (n=93) at baseline. The mean age of the people in the exercise group was 54.4 (SD 6.5) closely similar to that of the other groups: mean 52.2 (SD 8.2) for comparison group and 53.8 (SD:8.1) for the refusers. Overall, there were more men than women. In the exercise group and the off-site comparison group, 25% were employed; for the refusers, 42% were employed.

The median (IQR) of the ratings of perceived enjoyment for general exercise (received before the intervention) was 8(5-9). Adherence to the exercise training schedule was 85.2% (n=23). The program was well-received as shown by the ratings for the exercise enjoyment [median (IQR): 9 (8-10)]. No negative comments were received in the open-ended feedback obtained at the end of the intervention indicating good acceptability of the program.

Table 2 shows the extent of within-group change in the primary efficacy potential outcome, i.e., B-CAM, pre-and post-exercise training, for all three groups. Among the exercise group (n=27), average change in B-CAM post-exercise was near 0 (mean: 0.3; SD: 3.1) because 22.2% made a gain equivalent to ½ SD, 22% declined, and 55.5% remained unchanged. For the two comparison groups, the proportion making meaningful gains exceeded the proportion declining. When using reliable change as the estimator for response, the values for the three groups were: similar: 7.4% for exercisers, 7.8% for off-site comparison; and 5% for refusers).

Table 3 shows the outcome of change in verbal fluency, comfortable gait speed and dual-task gait speed among the exercisers. Before and after the exercise program, the mean number of words produced in a minute were higher than the Canadian norms, i.e., 17. Although majority (70%) of the participants exhibited no change in verbal fluency, 15% of the sample showed

meaningful improvements (> 5 words). However, when accounted for measurement error and practice effects, only 3.7% of the sample seemed to have benefited. The reliable change observed in comfortable gait speed and dual-task gait speed was 30% and 11.1%, respectively in the exercise group.

Table 4 presents the results of the physical performance measures pre-and post-exercise training in the exercise group. The SRM was highest for partial curl-ups (1.5; 95% CI:1.1 to 2.3) and lowest for averaged left grip strength (0.4; 95% CI: 0.1 to 0.9).

Table 5 presents the pre-and post-exercise performance in the platform measures. Median and interquartile range (IQR) values have been presented for the MHI and Vitality scores as they were not normally distributed. None of the platform measures in any of the groups benefited from the exercise training.

Discussion

This study was aimed at estimating the feasibility and efficacy potential of a 12-week structured exercise program in people with HIV. The exercise program yielded gains in aerobic capacity and motor performance as shown from the results of various physical performance tests (effect sizes ranging from 0.5-1.5) among the exercisers. The key efficacy potential outcome of this study was cognitive performance ascertained using B-CAM. It was found that little benefit was reaped on B- CAM in the exercise group (as reliable change was made by only 7.4% of the sample).

Within the exercise group, the improvement of various cardiorespiratory and physical performance measures post-training was in line with the extant literature in HIV (O'Brien et al., 2017; O'Brien et al., 2016; Gomes-Neto et al., 2015; Dolan et al., 2011; Nixon et al., 2010). A

meta-analysis reported significant improvement in peak aerobic capacity by 4.8 ml/kg/min (95% CI: 2.95 - 6.0) and muscular strength based on 7 studies with a combined aerobic and resistance training program (ranging from 6 to 24 weeks) compared to non-exercising controls (Gomes-Neto et al., 2015). In our exercise group, there was an increase of 4 ml/kg/min in predicted aerobic capacity post-exercise training. Exercise-induced cardiovascular and musculoskeletal adaptations are believed to promote cerebrovascular health, and ultimately cognition (Barnes & Corkery, 2018). However, the gains in cardiopulmonary fitness and physical performance did not yield much benefit on B-CAM among the exercisers in this study.

There is interest in intervention studies investigating the impact of exercise on cognitive functioning (as a primary outcome) in HIV. Most intervention studies in HIV do not report a positive influence on the cognitive outcomes (Schlabe et al., 2017; McDermott et al., 2017; Brown et al., 2016; Galantino et al., 2005). There was one randomized controlled trial (N=40) which produced evidence on the benefit of a twice-weekly combined aerobic and resistance training lasting 6 months on cognitive functioning in HIV men (Fillipas et al., 2006). Our feasibility study employed a lesser dose of exercise, i.e., 36 hours as compared to Fillipas et al., (2006) which implemented a higher dose (52 hours). The latter study used cognitive subscale of Medical Outcomes Study (MOS) HIV Health Survey which is a self-reported measure of health-related quality of life. Our study was relatively novel as compared to most exercise intervention studies in HIV as we employed a performance-based measure of cognitive ability.

The exercise program was developed based upon the recommendations which suggested that a combination of aerobic and resistance training for at least 6 weeks can confer benefits on cardiopulmonary and strength outcomes in HIV+ adults (Yahiaoui et al., 2012; Gomes-Neto et al., 2013). The HIV-specific exercise recommendations for improving neurocognitive outcomes

were not available before the conception of this study. In fact, no clear guidelines in the context of specific exercise parameters exist to date although some evidence has emerged in the aging literature. A recently undertaken systematic review of 98 clinical trials (with majority done with a rigorous methodology) found that the total intervention time was the most relevant correlate for better cognitive outcomes in older adults with and without cognitive impairment (Gomes-Osman et al., 2018). The median intervention time for studies with consistently positive outcomes was 52 hours. Among older adults with cognitive impairments (N = 13 studies), a meta-analysis revealed that exercise programs with a short session duration (<30 minutes) and high frequency (≥4 weeks) predicted higher effect sizes [0.43 (95% CI: 0.24-0.62)] and [0.50 (95% CI: 0.24-76), respectively] on cognitive outcomes (Sanders et al., 2019). It seems more rigorous research is required to determine the ample dose and regime that is productive in terms of cognitive functioning.

In this work, minimal important change (MIC) for B-CAM was highest among the refusers as 44% of the sample improved beyond ½ SD. However, controlling for the measurement error, only 5.4% of the sample exhibited reliable change in B-CAM. Reliable change in the comparison group was observed for 7.8% of the sample and 7.4% of the intervention sample. The exercise program seemed to have some favourable impact on verbal fluency in the exercise group. Four participants changed based on the MIC of >5 words. However, reliable change was achieved in only 1 participant. In the exercise group, improvements in dual-task gait speed were promising. 52% of the sample made meaningful gains of >0.1m/s with 11.1% of the sample showing reliable change. It is possible that exercising in a novel gym environment where new procedures (e.g., using elliptical machines, counting the sets and repetitions while lifting the weights) were involved and were potentially cognitively stimulating to a beneficial level. In people with stroke

(N=124), exercise training led to a small change in dual-task gait speed [mean difference (MD): 0.03m/s, 95% CI: 0.01 to 0.06] (Plummer & Iyigun et al., 2018).

Previous meta-analysis has reported clinically important change in the MHI-5 [weighted mean difference (WMD) = 11.58; 95% CI: 1.35 – 21.81] and Vitality subscale (WMD = 5.03; 95% CI: 1.33 – 8.72) with exercise in HIV (n=59; O'Brien et al., 2016). On the contrary, our study did not find improvements in the brain health outcomes of anxiety/depression and fatigue. Also, there were no benefits to self-perceived cognitive deficits measured by PDQ. All the platform measures were captured at 9 months intervals in the +BHN study (Mayo et al., 2016a). It is possible that participants completed the self-reported questionnaires when some time had passed after the exercise training so these findings may not reflect the immediate potential impact of exercise on these measures. However, these constructs take time to change and so having an evaluation at a later time provides an indication of any potential for sustained gain.

Like any other feasibility study, a key purpose of this study was to determine whether a full-scale clinical trial of the intervention in a similar setting would be feasible. Adherence to the intervention schedule was good and the ratings of exercise enjoyment post-training exhibited it was well-liked by the participants. There were no adverse events associated with our exercise intervention assuring it was a safe program for medically stable HIV+ adults. However, a full-scale trial may not be feasible with the exercise regimen employed in this study as it did not seem to benefit very many people: reliable change on B-CAM was observed in <10% of the samples in each study group. Assuming an 8% change in the exercise group, and a 4% change in a control group, 1000 people would be required (500 per group) to detect this change proportion [Relative Risk (RR): 2.0, 95% CI: 1.01 to 3.97)] (Armitage & Berry, 1994).

Additionally, sluggish recruitment despite good financial incentives ($123) could be another challenge questioning the practicality of a main study. Although the exact numbers are not known, out of the refusers (n=93) many participants were not interested due to the time commitment involved. There were also availability issues, and some were not so enthusiastic with the idea of doing exercise.

Furthermore, the exercise dose may also need revision in the light of recent evidence that programs of higher frequency, but of shorter session duration have a more favourable impact on cognition (Sanders et al., 2019). Before embarking on a definitive study, these factors would have to be considered.

Strengths and Limitations

This study used a single-arm, pre-post, design and, while there were two comparison cohorts, there was no randomly assigned control group. As this was a feasibility study, we wished to test the feasibility of the exercise program. The program was standardized and fully supervised providing ideal circumstances for feasibility testing. We did not use intention-to-treat approach and proceeded with per-protocol analysis for everyone who had adequate follow-up data. Each of the three groups had more men than women.

Conclusion

This feasibility study showed good adherence to the training schedule and acceptability of the 12-week intervention among people with HIV. Despite improvements in the outcomes of physical performance, there were no gains on the primary efficacy potential outcome of cognitive performance. A future definitive trial may not be feasible with a similar design as exercise-induced benefits in physical performance did not yield cognitive benefits in this study.

More research is required to establish if there is an optimal exercise dose for inducing change in cognitive outcomes in HIV.

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Table 1. Measurement strategy for efficacy potential of the 12-week exercise training

Outcome	Measure
Primary Efficacy Potential Outcome (Platform measure, 2 assessments – 9 months apart)	
Cognitive ability	Brief Cognitive Ability Measure (B-CAM; 0-36)
Other Brain Health Outcomes (Platform, 2 assessments – 9 months apart)	
Self-reported cognitive deficits	Perceived Deficits Questionnaire (PDQ; 0-80)
Anxiety/Depression	SF-36 Mental Health Inventory (MHI; 0-100)
Fatigue	SF-36 Vitality (0-100)
Motivation	Motivation ladder (0-42)
Exercise Specific Measures (0 and 12 weeks)	
Exercise capacity (kg/ml/min)	Step test
Functional walking capacity (m)	Six-Minute Walk Test (6MWT)
Seated leg power (W)	Power rig
Comfortable gait speed (m/sec)	GAITRite (4m track)
Fast gait speed (m/sec)	GAITRite (4m track)
Dual-task gait speed (m/sec)	GAITRite and naming fruit (4m track)
Hand grip strength (kg)	Jamar dynamometer
Core strength (#)	Push-ups and partial curl-ups
Other Cognitive Outcomes (0 and 12 weeks)	
Verbal (categorical) fluency	Number of unique animals generated in 1 minute

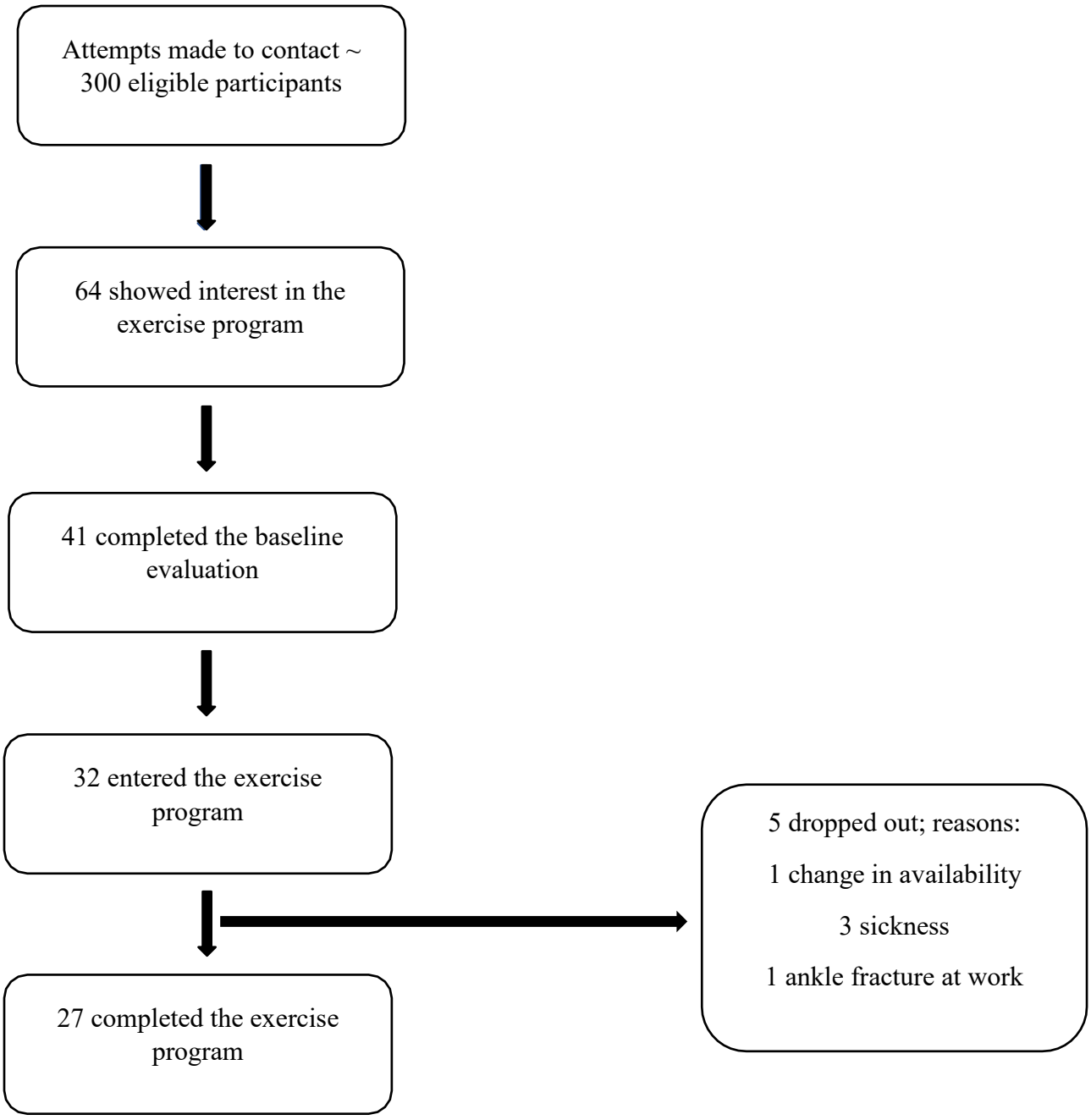

Figure 1. Flow of study participants into the exercise program

Table 2. Baseline characteristics of each of the three groups pre-exercise training

Characteristic	Exercise group (n=27)	Comparison group (n=114)	Refusers (n=93)
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)
Age (years)	54.4 (6.5)	52.2 (8.2)	53.8 (8.1)
Sex			
Men	23 (85.0%)	89 (78.0%)	83 (89.0%)
Women	4 (15.0%)	25 (22.0%)	10 (11.0%)
Current daily activity			
Employed	7 (25.9%)	29 (25.4%)	39 (42.0%)
Unemployed	10 (37.0%)	2 (1.7%)	13 (14.0%)
Disability/Retired/Other	10 (37.0%)	81 (72.8%)	41 (44.0%)
Years since HIV diagnosis	19.3 (7.0)	17.1 (8.1)	18.2 (7.2)
Smoking Yes No	 5 (18.5%) 21 (80.7%)	 37 (33.0%) 75 (67.0%)	 28 (30.43%) 60 (65.22%)

Table 3. Change in B-CAM pre-and-post exercise training in each of the study groups

Outcome	**Exercise group (n=27)** Mean (SD) / n (%)	**Comparison group (n=114)** Mean (SD) / n (%)	**Refusers (n=93)** Mean (SD) / n (%)
[a]B-CAM (0-36)			
Pre-exercise	20.3 (4.0)	16.1 (3.5)	17.0 (3.0)
Post-exercise	20.6 (4.6)	17.0 (3.6)	18.2 (3.3)
Change	0.3 (3.1)	0.9 (3.1)	1.2 (2.8)
Extent of [b]change n (%)			
Improvement: Change > 2	6 (22.2%)	42 (36.8%)	41 (44.0%)
Stable: Change -2 to +2	15 (55.5%)	53 (46.6%)	40 (43.0%)
Decline: Change < -2	6 (22.2%)	19 (16.6%)	12 (13.0%)
Reliable change: n (%)	2 (7.4%)	9 (7.8%)	5 (5.4%)

[a]Brief Cognitive Ability Measure; higher scores are better

[b]Based on ½ SD

Table 4. Change in verbal fluency, comfortable and dual-task gait speed in the exercise group (n=27)

Outcome	Mean (SD) or n (%)
Number of animals in a minute	
Pre-exercise [Norm 17 words]	19.3 (5.1)
Post-exercise	22.7 (5.3)
Change of [a]MIC: n (%)	4 (15.0%)
Reliable change: n (%)	1 (3.7%)
Comfortable gait speed	
Pre-exercise	1.2 (0.3)
Post-exercise	1.5 (0.2)
Change of MIC: n (%)	15 (55.5%)
Reliable change: n (%)	8 (30.0%)
Dual task gait speed	
Pre-exercise	1.1 (0.2)
Post-exercise	1.3 (0.4)
Change of MIC: n (%)	14 (52.0%)
Reliable change: n (%)	3 (11.1%)

[a]Minimal important change

Table 5. Physical performance pre-and post-12 weeks of exercise program (n=27)

Outcome	Pre-exercise Mean (SD)	Post-exercise Mean (SD)	Standardized response mean (SRM)	95% CI
Partial curl-ups (#)	8.9 (5.6)	18.0 (5.1)	1.5	1.12 to 2.25
Predicted VO_2max (ml/kg/min)	34.4(6.9)	38.4 (6.3)	0.9	0.61 to 1.37
Fast gait speed (m/s)	1.8 (0.3)	2.2 (0.4)	0.8	0.54 to 1.19
Seated leg extensor power (W)	204.0 (83.9)	240.3 (88.2)	0.8	0.41 to 1.19
Push-ups (#)	7.3 (5.2)	13.3 (6.3)	0.6	0.09 to 2.71
Six Minute Walk Test (m)	613.7 (83.9)	632.8 (55.2)	0.6	0.18 to 1.10
Averaged right grip strength (kg)	37.2 (7.8)	37.9 (8.2)	0.5	0.02 to 0.92
Averaged left grip strength (kg)	34.3 (8.5)	36.1 (9.3)	0.4	0.10 to 0.90

VO_2max = Maximal oxygen consumption

Table 6. Performance in brain health measures post-training in all the three groups

Outcome	Exercise group (n=27)		Comparison group (n=114)		Refusers (n=93)	
	Pre-Exercise Mean (SD)	Post-Exercise Mean (SD)	Pre-Exercise Mean (SD)	Post-Exercise Mean (SD)	Pre-Exercise Mean (SD)	Post-Exercise Mean (SD)
[a]PDQ (0-80)	35.3 (18.8)	34.7 (18.0)	43.9 (18.5)	42.9 (17.3)	36.0 (16.8)	34.5 (17.0)
[b]MHI (0-100)	[e]60 (28-76)	64 (44-80)	60 (48-80)	64 (48-80)	64 (48-78)	68 (48-80)
[c]Vitality (0-100)	[f]55 (47-77)	50 (35-75)	40 (35-60)	50 (30-65)	50 (35-70)	55 (40-70)
[d]Motivation (0-42)	27(12.0)	29 (11.4)	26.3 (11.9)	25.8 (11.9)	25 (11.8)	25 (11.1)

[a]Perceived Deficits Questionnaire; a score of 40 or more is considered to indicate cognitive impairment
[b]Rand-36 Mental Health Inventory; higher scores are better
[c]Rand-36 Vitality Subscale; higher scores are better
[d]Motivation (3 items); higher scores are better
[e]Median (IQR) presented
[f]Median (IQR) presented

Chapter 8: Integration of Manuscript III and IV

Research Objectives of Manuscript III

(i) To estimate the feasibility of a 12-week combined aerobic and resistance exercise program in individuals with HIV; and (ii) to estimate the extent to which participants changed cognitive ability, physical performance, and other brain health outcomes (self-reported cognitive deficits, anxiety/depression, fatigue and motivation) after 12 weeks of engagement with the structured exercise program.

Research Objectives of Manuscript IV

To estimate the extent to which pilot/feasibility studies in *Clinical Rehabilitation*: (i) addressed needed objectives; (ii) led to definitive trials; and (iii) whether the subsequent undertaking of a definitive trial was influenced by the strength of the evidence of outcome improvement.

During the planning of the feasibility study documented in the Manuscript III, I wondered whether there is any difference between pilot and feasibility studies as these terms are often employed interchangeably across the scientific literature. Also, I was inquisitive to know the destiny of the pilot studies in the field of rehabilitation once they are done. Are they valuable? Do they get followed-up in a definitive clinical trial? What exactly makes a study a 'pilot study' as it is a common practice for a study with a "small sample size" and/or lack of funds to be given this designation. These questions were pursued in the form of a systematic review of all 191 feasibility studies published in the journal of *Clinical Rehabilitation* since its inception. This journal was chosen as this manuscript was part of a series of papers celebrating the 30th anniversary of this journal. The following manuscript in this thesis addresses the aforementioned questions and sets out general guidelines for feasibility studies in the field of rehabilitation research.

Chapter 9: Manuscript IV

Where have all the pilot studies gone? A follow-up on 30 years of pilot studies in *Clinical Rehabilitation*

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Article

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Abstract

Introduction: Pilot studies are meritorious for determining the feasibility of a definitive clinical trial in terms of conduct and potential for efficacy, but their possible applications for planning a future trial are not always fully realized. The purpose of this review was to estimate the extent to which pilot/feasibility studies: (i) addressed needed objectives; (ii) led to definitive trials; and (iii) whether the subsequent undertaking of a definitive trial was influenced by the strength of the evidence of outcome improvement.
Methods: Trials published in the journal *Clinical Rehabilitation*, since its inception, were eligible if the word 'pilot' or 'feasibility' was specified somewhere in the article. A total of 191 studies were reviewed, results were summarized descriptively, and between-group effect sizes were computed.
Results: The specific purposes of piloting were stated in only 58% (n = 110) of the studies. The most frequent purpose was to estimate the potential for efficacy (85%), followed by testing the feasibility of the intervention (60%). Only 12% of the studies were followed by a definitive trial; <4% of studies had a main study underway or a published study protocol. There was no relationship between observed effect size and follow-up of pilot studies, although the confidence intervals were very wide owing to small number of trials that followed on.
Discussion: Labelling and reporting of pilot studies needs to be improved to be concordant with the recently issued CONSORT guidelines. Feasibility needs to be fully tested and demonstrated prior to committing considerable human and monetary resources.

Keywords

Rehabilitation, randomized controlled trial, controlled clinical trial

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Background

Clinical trials answer questions about deliberate interventions that are often innovations in treatment and the results are meant to inform clinical practice.[1,2] Because of the innovation, many of the details of a definitive trial are unknown before starting, and should be investigated systematically before committing to a larger study. Trials of rehabilitation interventions are particularly challenging as they often involve testing of interventions with different active ingredients.[3,4] How the multiple elements of the trial work together need to be tested, including the best way to identify participants, whether randomization is accepted, the processes around delivering the intervention, and the optimal control for the experimental intervention, to name but a few of the questions to be answered. Many trials suffer from recruitment challenges, high attrition rates because of tediousness or intolerable study demands[2] making it essential to identify these potential bumps in the trial road beforehand.

In the past, some authors have weighed in on definitions and purposes of pilot and/or feasibility studies.[5–7] The first consensus on the definitions of pilot and feasibility studies was published in 2016 and provided a conceptual framework to unify the disparate concepts that are grouped under feasibility or pilot studies.[8] Many pieces of research may need to be done before a main study can be justified, essentially to probe into the feasibility of various aspects of a study protocol. Important parameters, including recruitment rates, completion rates, adherence rates, and resources needed, that are crucial for designing a definitive trial, can be estimated through these preparatory studies.[7] However, if no evidence is provided to show that the intervention may produce some change in the outcome, with or without a control group, it is hard to judge the efficacy potential of an intervention. Both the processes planned for the trial and the potential for efficacy are necessary for a full trial to be feasible, but neither alone is sufficient.

The recently achieved consensus[8] is that 'pilot' studies fall under the dimension of 'feasibility' studies. Up to now, the terms 'feasibility' and 'pilot' have been used and misused in the medical literature, particularly when these terms have been used 'post hoc' to disguise underpowered main studies,[7,9] those studies with methodological limitations, or those not completed because of inadequate funding.[10]

Feasibility of processes and outcome potential are essential elements for funding of a clinical trial, but the vast majority of feasibility studies are hardly published.[4] Those that are published tend to be the ones with data reporting efficacy potential. Some reviews on the methodological quality of pilot (feasibility) studies have been undertaken[9,11–13] and their conclusions are summarized in Table 1. Overall, it has been observed that the pilot studies are frequently employed for hypothesis testing and feasibility of processes are rarely considered. Although follow-up is recommended, only a meagre proportion of preliminary studies have been pursued further in a confirmatory study.

Over the last few years, a major emphasis has been laid upon informing researchers about appropriate objectives[7,11,14] and methodological features of pilot studies.[7,14] Seven evidence-based objectives of conducting such studies have been identified:

1. to evaluate the integrity of a study protocol for a larger study;
2. to acquire preliminary estimates for sample size computation;
3. to test data collection questionnaires;
4. to test the randomization technique(s);
5. to estimate the recruitment and consent rates;
6. to test the acceptability of the intervention; and
7. to choose the most suitable outcome measure(s).[11]

The extent to which pilot studies in the rehabilitation literature live up to these expectations is unknown and is the topic of this review using the pilot/feasibility studies published in *Clinical Rehabilitation* over the past three decades as examples. The specific objectives are to estimate the extent to which the identified pilot/feasibility studies: (i) address needed objectives; (ii) lead to definitive trials; and (iii) whether the subsequent undertaking of a definitive trial is influenced by the strength of the evidence of outcome improvement.

Table 1. Summary of previous reviews on the practices associated with pilot studies.

Study reference	Number and type of journal articles included	Time period of review
Lancaster et al.[11]	90; Four general clinical journals, *British Medical Journal* (BMJ), *Lancet, Journal of the American Medical Association* (JAMA), and *New England Journal of Medicine* (NEJM), and three subject-specific journals, the *British Journal of Cancer* (BJC), *British Journal of Obstetrics and Gynaecology* (BJOG) and the *British Journal of Surgery* (BJS)	2000–2001
Only four articles stated that the pilot study was in preparation for a clinical trial; >50% of the articles concluded that a further study was required.		
Arain et al.[9]	54; Follow-up to previous review;[13] describes same journals as given above, with the addition of 12 reports from the UK Clinical Research Network Portfolio Database	2007–2008
Of the studies, 48%were identified as 'pilot' and the rest were 'feasibility' studies; 81% focused on hypothesis testing and 81% highlighted the need for further study. Only eight of the 90 articles (9%) identified by the previous review[11] were followed up in a subsequent larger study.		
Shanyinde et al.[12]	50; Pilot and feasibility randomized controlled trials from EMBASE and MEDLINE databases	2000–2009
In only 56% of studies, (95% confidence intervals 41% to 70%) were methodological issues discussed in adequate details, 18% (95% confidence interval 9% to 30%) mentioned future trials in the discussion section, and only 12% (95% confidence interval 5% to 24%) of investigators were actually undertaking a subsequent trial.		
Kannan and Gowri[13]	93; Indian journals of allopathic medicine, dentistry, and complementary and alternative systems of medicine	Between January and December 2013
None of the studies presented the reason for piloting; none of them discussed feasibility; 2/3 of the articles did hypothesis testing and inferred the significance of differences between the groups and none of these studies mentioned power for these contrasts.		

Methods

Eligibility criteria

Trials published in the journal *Clinical Rehabilitation*, since its inception, were eligible if the word 'pilot' was specified anywhere in the article by the authors. Also eligible were research publications labelled as 'feasibility studies', 'preliminary studies', and 'proof-of-concept studies' as these terms are often used interchangeably with 'pilot' studies.[9,14–16] For the purpose of this review, the delineation between pilot and feasibility studies was not made, although the consensus definition[8] considers all preparatory studies as 'feasibility'. The consensus reserves the term 'pilot' for those small-scale studies that have a specific design feature (either randomized or not) that test some or all aspects of a future trial. We use the term 'pilot' study to refer to the studies reviewed here and the term 'feasibility' if the authors of the chosen articles used this term rather than 'pilot'.

Search strategy

This study was embedded within a larger study reviewing the methodological features of trials published over the past 30 years in the journal *Clinical Rehabilitation*.[3] The search strategy has been described previously[3] and yielded 581 clinical trials that had a control group, randomized or not. Of these trials, 191 articles were identified to be pilot or feasibility studies by one of the 23 reviewers conducting the comprehensive data abstraction for the larger study.

Data abstraction

For the review of full clinical trials,[3] a data abstraction form was devised and much of the data elements related to both full and pilot trials. A separate data extraction form was created specifically for pilot studies to include additional fields for: (i) location of declaration of the 'pilot' nature of the study; (ii) whether the authors stated the purpose of

the piloting; (iii) the reason(s) for the piloting; (iv) inferring the reason(s) if not clearly mentioned; (v) whether the study was followed up in a definitive clinical trial; (vi) whether the sample size calculation was made for the future definitive study; and (vii) data for calculating effect size for the between-group comparisons.

Both data abstraction forms included information on sample size at randomization and at the end of intervention and, hence, this information was abstracted by two reviewers. For the other fields not duplicated for full and pilot trials, the data extraction was conducted by one reviewer (NK), areas that lacked clarity were discussed with a senior reviewer (NM), and a decision was made as to the data to be abstracted. The information on the follow-up of a pilot study was obtained by examining its citations in SCOPUS. Additionally, the corresponding author of each article was sent an email inquiry to verify if a definitive study was undertaken. If an article did not provide an email address for correspondence, the follow-up status was decided based upon SCOPUS entries.

Data analysis

Frequency distributions and means and standard deviations were used to describe the features of the pilot studies. Between-group effect size was computed for each pilot study using the standardized mean difference. Effect size was not calculated for studies that provided only median and interquartile range values. Based on the distribution of data, effect size was classified into six categories ($\leq$0.1; >0.1 and $\leq$0.2; > 0.2 and $\leq$0.5; 0.5 and $\leq$0.8; >0.8 and $\leq$2.0; and >2.0). Logistic regression was used to estimate the association between the observed effect size and follow-up of pilot studies, with the effect size category $\leq$0.1 as the referent. Odds ratio (OR) and associated 95% confidence intervals (CI) were calculated. The pilot studies were divided into three eras based upon the year of publication (<1999; $\geq$1999 and $\leq$2009; and >2009 to $\leq$2015). Chi square analysis was employed to estimate the influence of era on the association between the strength of effect and follow-up. All analyses were conducted in SAS 9.3.

Results

A total of 191 pilot studies were identified for the time period 1987 to March 2015: seven (4%) before 1999; 71 (37%) between 1999 to 2009; and 113 (59%) after 2009 and up to the year 2015. Table 2 shows the key characteristics of the chosen studies. Pilot status was declared most often in the title (87%) and abstract (68%). The objective indicated pilot status in only 54% of studies. The purpose of piloting was specified in only 58% (n = 110) of the pilot studies. Among these 110 studies, the most frequent purpose was to estimate the potential for efficacy (85%) followed by testing the feasibility of the intervention (60%). Feasibility of outcome measures, safety of intervention, sample size computation, and feasibility of recruitment rates were reported as one of the main objectives of piloting in <11% of studies. Other feasibility reasons that were identified included estimating retention rates[17–20] and testing the acceptability of intervention.[20–23]

For the 42% of studies (n = 81) that did not declare a clear purpose for piloting, inference was based upon the information provided in the manuscripts. Estimation of efficacy potential (89%) and feasibility of intervention (15%) were the most common reasons followed by feasibility of recruitment rates and timing of intervention effect on outcomes.

Almost half of the studies used the terms ‘pilot’ and ‘feasibility’ interchangeably and only 6% of the 191 studies were uniquely labelled as ‘feasibility’ studies. Only 34% of the studies had done a power calculation for a future definitive clinical trial.

Table 3 indicates the sample sizes and drop-out proportions. The average sample size was 31 with a large range from 7 to 120. The proportion of drop-outs averaged 3% with a range from 0% to 31%.

Table 4 shows that, of the 191 pilot studies, 12% (n = 23) were followed by a definitive clinical trial; an additional small percentage ~3.5% (n = 7) of studies had a main study underway or a published study protocol. The remaining (85%;

Table 2. Characteristics of the 191 pilot studies included in the review.

Characteristic	*N*	%
Location of declaring 'pilot'		
Title	168	87
Abstract	131	68
Title or abstract	184	96
Introduction/objective	104	54
Study design	78	41
Results	7	4
Discussion	105	55
Conclusion	49	26
Purpose of 'piloting' declared		
Yes	110	58
No	81	42
Purpose of 'piloting' declared as[a]		
Feasibility of recruitment rates	9/110	8
Compliance or adherence rates	4/110	4
Timing of effect of an outcome	0/110	0
Feasibility of intervention	66/110	60
Feasibility of outcome measures	12/110	11
Estimation of efficacy potential	94/110	85
Safety of intervention	11/110	10
Computation of sample size	10/110	9
Purpose inferred when not declared as[a]		
Feasibility of recruitment rates	5/81	6
Compliance or adherence rates	1/81	1
Timing of effect of an outcome	5/81	6
Feasibility of intervention	12/81	15
Feasibility of outcome measures	0/81	0
Estimation of efficacy potential	72/81	89
Safety of intervention	2/81	2
Computation of sample size	1/81	1
Studies labelled as 'feasibility'	12	6
Power calculation made for a definitive clinical trial	64	34

[a]Studies could have more than one reason for 'piloting'.

Table 3. Distribution of sample size in the included 191 studies.

	Total sample size	Drop-out proportions
Mean (SD)	31 (18.3)	3 (4.6)
25 percentile	20	0
50 percentile	28	2
75 percentile	40	5
Range	7–120	0–31

Table 4. Follow-up status of the 191 pilot studies.

	N	%
Follow-up of pilot studies		
Completed	23	12
Trial underway or completed but not yet published	4	2
Published protocol available	3	1.5
None	162	85
Email contact available	173	90
Outcome of email contact		
Undelivered	76/173	44
Unanswered	26/173	15
Answered	71/173	41
Reasons presented for no follow-up		
Lack of funding	9/17	53
Results confirmed by another team	2/17	12
Pilot work conducted as a part of student's thesis	2/17	12
Principal investigator no longer doing research	2/17	12
Product to be evaluated not made available	1/17	6
Power analysis indicated recruitment not feasible	1/17	6

$n = 162$) did not appear to have had any further follow-up. There was no effect of era on follow-up status (data not shown). Also demonstrated in Table 4 is the follow-up process. A total of 173 emails were sent, enquiring about follow-up status. Of these, 44% ($n = 76$) were not delivered, 15% ($n = 26$) were unanswered, and the remaining 41% ($n = 71$) were answered. Only 17 of the corresponding authors provided a reason for non-pursuance of their pilot work. The commonly encountered cause for no follow-up was the lack of a funding resource.

Table 5 presents the association between effect size and follow-up of the 144 studies that presented sufficient data to allow computation of between-group effect size. Logistic regression analyses demonstrated that in comparison with the lowest effect size, i.e. Cohen's *d* less than 0.1, there was a tendency for a lower odds of follow-up for studies with effect sizes between 0.8 and to 2.0 to be followed up (OR 0.69, CI 0.08 to 5.46). Studies with effect sizes greater than 2.0 had the same odds of

Table 5. Association between effect size and follow-up of 144 studies.[a]

Effect size (Cohen's *d*)	Total number of studies	Number of studies with follow-up	Odds ratio	Confidence intervals
	N (%)	*N* (%)		
No data	47 (25)	8 (17)		
<0.1	18 (13)	2 (11)	Referent	
>0.1 to ⩽0.2	21 (15)	6 (29)	3.20	0.05 to 18.38
>0.2 to ⩽0.5	33 (23)	5 (15)	1.42	0.24 to 8.23
>0.5 to ⩽0.8	28 (19)	5 (18)	1.73	0.29 to 10.1
>0.8 to 2	25 (17)	2 (8)	0.69	0.08 to 5.46
>2	19 (13)	2 (11)	0.94	0.11 to 7.49

[a]Studies with sufficient data to estimate between-group effect size.

follow-up as those with very small effect sizes, <0.1 (OR 0.94, CI 0.11 to 7.49). However, none of the associations were statistically significant as the CIs included the null value of 1.0.

Discussion

This article reviewed the state of pilot/feasibility studies published in *Clinical Rehabilitation* since its inception (1987). During the 30-year time period, 191 pilot studies were published, while the corresponding number of full trials was 390, indicating the importance of pilot trials in the rehabilitation literature. The specific purposes of piloting were not always stated. In fact, only 58% ($n = 110$) of the studies clearly declared what was being piloted. The most frequent purpose was to estimate the potential for efficacy (85%) followed by testing the feasibility of the intervention (60%). The terms 'pilot' and 'feasibility' were often used interchangeably to describe studies designed to inform future trials. However, only 12% of these studies were followed by a definitive clinical trial and <4% of studies had a main study underway or a published study protocol.

This review identified, in one journal only and over 30 years, that one-third of clinical trials were pilot trials. An Ovid MEDLINE search of the term 'pilot study' in the titles of the research articles published over only 1 year (2014) yielded 6002 records, indicating the widespread use of the term. However, the previous corpus of reviews on the state of pilot studies (see Table 1) has indicated that not enough justice has been done to their conduct or follow-up.

What should be the focus for the next 30 years of pilot studies?

Label pilot studies correctly. The recently devised conceptual framework for the definitions of preparatory studies[8] and the CONSORT reporting guidelines for pilot and feasibility studies[24] should be followed. As proposed by the conceptual framework, when there is uncertainty about the feasibility of a future randomized controlled trial, a 'feasibility' study should be carried out.[8] Not addressed by this framework[8] are internal pilot studies, which are fundamentally part of the definitive trial, but are mainly used to revise the sample size estimates upwards based on initial effect size estimates.[11] In rehabilitation, these internal pilot studies would be rare.

As per the framework, 'feasibility' is an umbrella term that encompasses three types of preparatory studies.[8] Randomized pilot studies are those in which a future definitive clinical trial involving randomized study groups or its components are investigated on a miniature scale. Non-randomized pilot studies are similar to the randomized pilot studies except these do not include randomization of study participants. Another category includes feasibility studies that are not pilot studies. These endeavour to test

whether some component of a future trial can be executed and may address the development of an intervention in some manner. However, these do not involve implementing an intervention or other components associated with processes that may be needed to be carried out in a future main study.[8]

This review found only 6% of the included studies were labelled as 'feasibility'. Mostly, the terms 'pilot' and 'feasibility' were employed without any distinction between the two. Consistency in the terms used to label the preparatory studies should improve with the advent of the consensus definitions[8] and the CONSORT reporting guidelines for pilot and feasibility studies.[24] Also, declaration of pilot/feasibility status both in the title or abstract is deemed useful for indexing purposes and for an easy identification in the electronic database searches.[7,8] This is recommended by the CONSORT guidelines[24] as well. Most of the reviewed pilot studies complied with this recommendation, whereas a minor proportion designated the status in the conclusion section only. Better labelling of the pilot studies can improve their impact and visibility.

Distinguish pilot studies from small clinical trials. It has been recognized that authors designate small clinical trials as 'pilot' studies 'post-hoc' when it is clear that they cannot reach a definitive answer from the data accrued; some reviewers or journal editors also insist on this labelling, although the trial was not developed as 'pilot'.[12] Consequently, small trials primarily estimating efficacy end up being labelled as 'pilot' without the objectives compatible with pilot/feasibility status. This practise has also been adopted by *Clinical Rehabilitation*. As suggested by Sackett and Cook over two decades ago,[25] methodologically sound small clinical trials can lead to vital lessons. They have a potential to challenge traditional therapeutic judgements that have not been put to investigation before. Therefore, they should be labelled as such and not disguised as 'pilot'. Many prominent journals, including *Clinical Rehabilitation*, do not yet have an existing policy for the conduct and reporting of pilot studies.[9] Changing journal policy about reporting of pilot studies would help improve the situation. Recently, a new open access journal called *Pilot and Feasibility Studies* has been created to ensure that all foundational work conducted for large-scale studies can be brought to light.[26]

Focus on the required objectives of pilot/feasibility studies. Based on the pilot studies published in *Clinical Rehabilitation*, it was found that most were undertaken with specific objectives of estimating the potential for efficacy and testing the feasibility of intervention. Indicators of feasibility did not receive much attention in the reviewed studies. This is in line with the previous reviews.[12] One aspect of feasibility that is unique to rehabilitation studies is the feasibility of the measurement strategy. Unlike the pharmacological trials where the outcomes are mostly directly measured, rehabilitation studies tend to have multiple outcomes that are a mix of directly measured as well as patient-reported, and can also be measures of complex, theoretical constructs, such as health-related quality of life.[4] Therefore, it is crucial to test the feasibility of the outcome measurement strategy to avoid missing data arising from a measurement approach that is too burdensome for respondents. As outlined by one of the most comprehensive guides on pilot studies,[7] objectives should address process (e.g. recruitment, refusal, retention, and adherence rates), resources (e.g. adequacy of equipment), and management (e.g. data handling) issues. Our review found scant emphasis on these objectives (see Table 2). Including all this information in the pilot phase not only facilitates the conduct of a full-strength trial, but also leads to a more competitive proposal for funding purposes.[10,27]

Justify the rationale for chosen sample size. In terms of sample size, there was an average of 31 participants in the pilot studies reviewed in this manuscript, with a wide range from seven to 120 participants. A group of researchers conducted an audit of sample sizes in pilot studies carried out in the UK and reported a comparable range, from eight to 114 participants. On the other hand, feasibility trials had a minimum of 10 to a maximum of 300 participants.[28] Several authors have made recommendations for sample size to be included. For

example, there is a general rule of thumb to recruit at least 30 participants or higher for parameter estimation,[29] whereas another researcher[30] suggests recruiting at least 12 participants per study group. To minimize the imprecision surrounding the estimation of standard deviation, a total sample size of 70 participants is deemed necessary in a study with two treatment arms.[31] Although rationale for establishing sample size is important to be included, there is a view that a formal calculation may not be appropriate.[28] For example, if the intention is to support feasibility of the main trial from adherence or completion rates from a pilot, the confidence one can have from these pilot estimates is a function of the pilot sample size. If a pilot study of 30 people has observed a completion rate of 80%, the 95% confidence around this proportion is 63% to 90%. This means that a definitive trial is more likely to have a lower completion rate than higher; even increasing the pilot size to 50 participants would not yield much greater estimation confidence (95% CI 67% to 90%).[32]

Use the correct analytic approach. It is essential to underscore that pilot studies are not intended for testing hypothesis,[16] however, they can certainly indicate the potential for efficacy,[24] which would support pursuing a definitive trial. Between-group comparisons should not be performed, as the study, by design, is not powered for this contrast.[16] Ideally, the authors should report descriptive statistics, point estimates, and CI for the effect observed.[11] As recommended by Lee and his colleagues,[33] CI should be interpreted in relation to a priori-determined minimally important differences (MID).[16,34]

Effect size is the parameter that best indicates the potential for efficacy.[24] Pilot studies with effect sizes in the small or trivial range could be considered to provide weak evidence of efficacy potential. It is vital to mention that only 144 studies could be included in the main analysis, as the rest of the studies did not provide data for the computation of the effect size. Most of such studies presented either median and interquartile range values or had included no data that could lead to the effect size estimation. In the future, researchers need to ensure that ample data are given in the manuscript. Approaches to statistical analysis that go beyond simply reporting mean changes, such as defining responder-status, are also recommended.[3] This particular approach involves dichotomizing a continuous primary outcome measure into 'responders' and 'non-responders' based on a magnitude of effect deemed to be important. This information can be used to enhance interpretability of the data collected and can provide preliminary estimates of number needed to treat.[10]

Improve on the reporting of pilot studies. The recently generated reporting guidelines for pilot and feasibility studies, produced as an extension for the CONSORT statement,[24] should be implemented, however, additional emphasis is likely needed for rehabilitation studies. Most rehabilitation interventions require pilot testing as these interventions tend to be complex owing to the need for tailoring to the individual, their multi-modal nature, the number of other active ingredients,[4] such as people, setting, and attention, that need to be balanced by the control situation,[3] and the difficulty in masking research personnel and participants[2] when assessing outcomes. In these complex situations, pilot studies serve a crucial role of ensuring a robust methodological approach in a subsequent definitive trial. There is some guidance available on how to approach pilot and feasibility studies associated with occupational therapy interventions systematically.[4] To improve the reporting standards in rehabilitation in general, the authors of pilot studies should clearly incorporate information on the success of randomization, suitability of control condition, optimal recruitment strategy, drop-out rates, intervention integrity (i.e. if the intervention is delivered as per the original plan to each participant),[35] adverse events, and power calculation for a full-strength trial, in addition to the other aspects of feasibility. Appropriate objectives should be stated explicitly. The authors should acknowledge that the validity of findings could be dubious if they employ inferential statistics in a pilot study with a small sample size.[16] And for future studies, the data collected from pilots serve two purposes: Inform the need for a future trial and the determination of sample size required to confirm the hypothesis.

Justify the need for a further trial, and do it. One of the main objectives of this particular review was to estimate the extent to which the pilot study outcomes influenced the undertaking of a subsequent definitive trial. Only a small proportion of pilot studies were eventually followed up and these findings concur with previous reports.[9] Contrary to the usual expectations, it was found that the strength of effect observed in pilot studies was not associated with the follow-up status. The thinking here was that if the effect was nil or close to nil, a main trial may not be justified as there was no evidence for efficacy potential. On the other hand, pilot studies with very large effect sizes may also not progress to the definitive stage as the authors and funders may think it is no longer ethical to offer the control condition. Cronbach counselled against thinking that the results of pilot studies will be replicated in a larger study by introducing 'superrealization bias'. It is an outcome of the observation that in small scale studies, the researchers are capable to attain a high quality implementation which could never be achieved on a larger scale.[36] Only one pilot study was identified as addressing the issue indicating that the effect size found in the small pilot on a walking intervention for cancer fatigue was 'over optimistic'.[37]

Funding agencies often require that a pilot study is truly encouraging to persuade funders that a full strength clinical trial should be carried out.[10,38] Although the reasons for not being able to conduct a subsequent trial were not probed in this review, two of the corresponding authors pointed out that lack of funding hindered them from pursuing their work. Among other reasons, was change-over in personnel, particularly if the pilot was undertaken by a trainee.

Be vigilant while calculating sample size needed in next trial. Over 60% of reviewed studies did not provide sample size estimates for a subsequent full-scale trial using the data accrued from the pilot. Although sample size computation for a future trial is considered one of the fundamental objectives of pilot studies, it is worth noting that small datasets tend to yield imprecise effect size estimates, so the sample size estimates should be interpreted with caution.[28,38,39] In an observational study by Salbach and her colleagues,[40] the responsiveness of gait speed over time had an effect size of 1.22 with CIs (0.93 to 1.50). With a total of 50 participants, the width of the CI is quite wide and choosing the mid-point rather than the lower bound would greatly affect the sample size projections. Sample size estimates should not be based solely on the size needed to reject the null hypothesis (no effect), rather the size needed to reject a trivial alternative. This requires estimating sample size for a desired CI, one that excludes an effect of smaller than say 0.2 of a standard deviation (Cohen's effect size of 0.2).

Limitations

The studies incorporated in this review were acquired from a companion review of clinical trials.[3] An independent, systematic search of pilot/feasibility studies published in the journal was carried out subsequently and identified no additional studies. There is a likelihood of reviewer bias as not all elements of data abstraction were validated by a second reviewer. Also, it is possible that the information on the follow-up of pilot studies may not have been captured correctly, as citation entries may not be updated in SCOPUS. However, email enquiries were sent to the corresponding authors for the information on follow-up. Moreover, the studies that had no citations in SCOPUS were also searched in PubMED.

Although feasibility and pilot studies build a rich groundwork for definitive clinical trials, the practise surrounding their conduct and reporting needs to be bettered. For clarity and uniformity in the definitional context, the recently devised framework[8] for preparatory studies should be implemented. The notorious tradition of presenting the small clinical trials as pilot studies on account of their meagre sample size or other flaws should be avoided. Researchers need to ensure that methodologically sound pilot studies are undertaken and multiple aspects of workability of study protocol are investigated so that potential bumps in the road can be dealt with before embarking upon a full strength clinical trial.

Key messages

As there is likely considerable uncertainty when planning a full-scale trial of a rehabilitation intervention, feasibility needs to be tested and demonstrated prior to committing considerable human and monetary resources.

Feasibility is the overarching term encompassing: (i) pilot trials (randomized or not) testing both the intervention and other aspects of the trial process; and (ii) other feasibility studies that mainly test a process or may address development of an intervention.

The recently issued reporting guidelines for pilot and feasibility studies need to be followed by researchers, reviewers, and journals alike.

Small studies or studies that go wrong should not be labelled 'pilot' after the fact.

Pilot studies should fully describe the distribution of the sample on all outcomes at all time points, and provide point estimates of change with CIs rather than only a *p*-value.

Effect sizes estimated from pilot studies should be interpreted as potentially over-optimistic and power calculations should be adjusted accordingly.

Conflict of interest

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Chapter 10: Conclusion

The overall purpose of this thesis was to contribute evidence towards the role of cognitive reserve in protecting cognitive performance in HIV. The thesis comprised four manuscripts. Three manuscripts specifically pursued this purpose. The fourth manuscript arose to address some of the questions that lingered during the inception stages of the feasibility study covered in the third manuscript.

The key literature on cognitive reserve and cognitive performance in HIV was systematically addressed in the first manuscript (Kaur et al., 2019). This work facilitated the development of a framework for cognitive reserve and its relationship with brain pathology and consequences to cognitive performance and function in everyday life. This framework, presented below, guided subsequent phases of this thesis (Ravitch & Riggan, 2016).

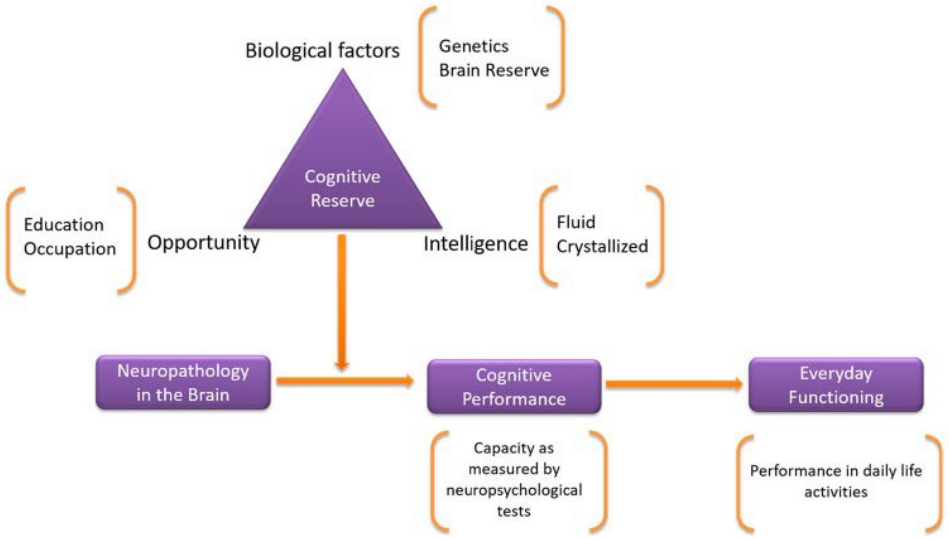

Figure 1. Hypothesized relationship between cognitive reserve and cognitive performance

The meta-analysis pooling data from 10 studies yielded an estimate of the strength of the association between cognitive reserve and cognitive ability. Cohen's *d* effect size of 0.9 translated to a correlation coefficient of 0.4. This work brought the heterogeneity across this literature to the surface. Although the source of heterogeneity was not verified due to methodological constraints, statistical heterogeneity was overwhelming in addition to the expected sources (including variations across the samples studied, the cognitive ability outcome measures used, and the operationalization of cognitive reserve). Lack of readily usable parameters that could contribute to a meta-analysis presented an arduous task as 9 out of the 10 studies were affected by this issue. A common practice is to abandon the meta-analysis approach. However, under the guidance of an expert team of a statistician and an epidemiologist a solution to harmonize the available parameters was found to derive a pooled estimate for the relationship between cognitive reserve and global cognitive performance. Although statistical heterogeneity complicated the estimation of the patterns of association between cognitive reserve and individual cognitive performance, this process served as an excellent learning experience from a methodological perspective.

The lessons reaped from this work affirmed some of the conclusions that are already prominent in the geriatric literature. For example, the latent construct of cognitive reserve was operationalized by a variety of cognitively stimulating activities performed over the lifetime of an individual. As identified by a recently published white paper on cognitive reserve (Stern et al., 2018), there are also a myriad of ways in which this concept has been operationalized in HIV. Concordant with the recent trends of measurement (Lojo-Seoane et al., 2018), a combination of multiple indicators is being employed in HIV as compared to reliance on a single indicator. However, there seems to be no consensus on the optimal combinations and methods of measuring various indicators of cognitive reserve. Unless a consensus is reached in this context,

the heterogeneity caused using a wide array of measures will remain a limitation.

Educational attainment, occupational complexity, and IQ are the commonly employed indicators but the neuroHIV literature has not entertained engagement in recreational activities as an indicator of cognitive reserve. This aspect was addressed in the second component of this thesis. The dataset on 856 HIV+ individuals from four Canadian cities provided an opportunity for this area to be investigated. Leisure activities seemed to offer a promising avenue for potential benefits to cognitive performance in HIV. It was particularly found that any level of engagement in visual arts (e.g., painting, drawing, photography), games, music, and travel outside the continent extended benefit to cognitive ability in HIV.

Education and occupational attainment are two indicators that are relatively "fixed" by the time one reaches adulthood in most individuals. It may not be a realistic option to manipulate these sources of cognitive reserve by advising individuals to acquire more education or acquire occupations with higher complexity. Rather a deliberate adoption of leisure activities could be one feasible strategy for gains in overall cognitive performance especially in the mid-adulthood. These leisure activities could be a more accessible "source of cognitive reserve" and could potentially be integrated into lifestyle-modification interventions.

The development of the weighted index (CRI-HIV) in Manuscript II was based on the formative measurement model which suggested that cognitive reserve is built by various indicators. Unlike most available indices of cognitive reserve (Nucci et al., 2011; Valenzuela & Sachdev, 2007), the index produced in this thesis was derived by considering the differential impact of indicators that were included in +BHN study specifically for this purpose by its investigators. As the literature has not converged on the relative impact of different indicators on cognitive performance (Lavrencic et al., 2017), the quantification of the index was driven by the relative contributions

of the available indicators in the +BHN dataset. Previous methods for developing indices have mostly assumed equal weighting (Valenzuela & Sachdev, 2007; Chan et al., 2018). Weighted indices have been developed in many other contexts (Mascarella et al., 2019; Noble et al., 2014; Tessier et al., 2008; D'Agostino et al., 2008; Deyo et al., 1992) and the standard methodology was applied here to develop the CRI-HIV.

The regression parameters from the logistic regression models were used to derive the scoring algorithm for each indicator of cognitive reserve. The odds ratios were not used for this purpose as it is only the regressions coefficients that are additive (Mehta et al., 2016; Harrell, 1996). Therefore, the regression coefficients were summed together to give a single numeric score for cognitive reserve. The measure of cognitive ability (B-CAM) employed in this study did not have any published cut-off points for discrimination between high and low cognitive performance. Instead, the highest quartile was used to define people who are likely to have a high level of cognitive ability.

Cognitive reserve is potentially an important prognostic construct in explaining cognitive outcomes. Interventional studies often identify prognostic factors in order to make sure that groups are balanced on these important factors. Having multiple prognostic indicators makes it difficult to consider these either in the design stage of a trial or during analysis (Cleophas & Zwinderman, 2007). It is statistically inefficient to consider individual indicators separately. CRI-HIV will serve as a useful research tool for purposes of adjustment in studies of interventions targeting cognitive outcomes.

As hypothesized by the cognitive reserve framework presented in Manuscript I, the relationship between cognitive reserve and cognitive performance is not direct but rather cognitive reserve

mediates the effect of brain pathology on performance. Thus, the relationship was hypothesized to be moderate at best. From the systematic review presented in Manuscript I, the estimated association was moderate (r = 0.4; N=1073). The association between cognitive reserve and cognitive performance in the +BHN cohort studied here was closely similar (r = 0.3; N=856). Similar results have been observed in the geriatric literature where a meta-analysis found a comparable association (r=0.31) (Opdebeeck et al., 2016) between the two constructs.

The CRI-HIV index was not tested for predicting change in cognitive ability. There are many methodological considerations related to change. In this context, the main consideration was that there was no true baseline as this was a prevalent cohort, not an inception cohort. Change may have already occurred (Glymour et al., 2005) from HIV infection to study entry, which was on average 18 years. The change over 3 to 4 years was likely minor or not detectable. This type of bias is termed incidence/prevalence bias where outcome is ascertained late after "exposure" allowing for change to have already occurred (Sackett, 1979). Therefore, the index was evaluated against the post-B-CAM value as to contribute evidence for its convergent validity.

The +BHN longitudinal study was designed as a cohort multiple randomized controlled trial (cmRCT) (Mayo et al., 2016; Relton et al., 2010) which allowed a sampling strategy to identify participants eligible for feasibility studies of promising interventions. Under this design, each feasibility study was determined to have a sample of 30 subjects. One of the feasibility studies (Elridge et al., 2016) was a structured exercise program of 12 weeks duration (Manuscript III). Physical activity is seen as a contributor of cognitive reserve (Najar et al., 2019; Mortimer & Stern, 2018). It is believed that exercise may benefit cognition through direct or indirect pathways (Fazeli et al., 2014, Lee et al., 2011). It can directly promote the upregulation of various neuronal growth factors that are responsible for neurogenesis, neuronal survival and

angiogenesis. For example, aerobic training has been associated with enhanced levels of brain-derived neurotrophic factor (BDNF) (Seifert et al., 2010), whereas resistance training produces rise in the levels of insulin-like growth factor 1 (IGF-1) (Cassilhas et al., 2007). Indirectly, exercise can lead to improved general health with increase in aerobic capacity, muscle strength and muscle mass, and reduce atherosclerosis. These changes result in better insulin control and attenuated inflammation (Ortega et al., 2015). Additionally, the neurological literature has revealed that environmental enrichment promotes neuroplasticity of the brain (Kolb et al., 2010; Petrosini et al., 2009). Therefore, it was expected that engagement in a novel environment with a specialized gym equipment would yield some cognitive benefits. The results of the specific exercise program evaluated in this thesis showed benefits for physical capacity. However, these gains did not translate to changes in cognitive performance as measured by B-CAM.

It is important to comment on whether this feasibility study (Manuscript III) should be pursued in a full-strength definitive trial. There are various factors that need to be considered while answering this question. Firstly, B-CAM used to capture cognitive ability in this study is a relatively new performance-based measure. Although developed using modern psychometric methods to produce a continuous score of cognitive ability, it has not been widely used. However, standard neuropsychological tests [Corsi block task (forward and backward), mini Trail-Making Test B, Eriksen flanker task, fluency and recall of a list of 8 words] have been included in the B-CAM (Brouillette et al., 2019). It is a computerized program that can be administered without the need of correction for practice effects; its administration and scoring takes under 40 minutes providing greater benefit for population health care research and clinical use. Also, it can be used for samples that vary demographically, and different raters can administer the test without influencing the results (Brouillette et al., 2019). From the feasibility perspective, adherence and acceptability of the exercise intervention were excellent. However,

the recruitment of participants was slow and laborious. A future study would have to take into account the likely burden this could have on the available resources. Also, one should not overlook the fact a high level of implementation might not be possible in a large study (super-realization bias) but it is rather achievable in a feasibility study of this scale (Cronbach et al., 1980). Another crucial question one needs to pose is whether there was any signal for efficacy potential, i.e., change in the B-CAM. As there were no major gains in the B-CAM, it does not favour the undertaking of a definitive trial. Future exercise regimens should be designed keeping in mind the recently emerged evidence on the specific exercise parameters that have profited cognition in the geriatric populations (Gomes-Osman et al., 2018).

The last component of this thesis addressed the fate of feasibility studies as the thesis contained one such study. While not linked to cognitive reserve in particular, it was connected in terms of the study design implemented in the Manuscript III. One of the objectives of this study was to estimate whether the follow-up of a feasibility study was affected by the effect size observed. It was found that the effect size did not drive the follow-up. This work was instrumental in framing optimal outcomes for the feasibility study (Manuscript III) and it set out the vital areas of focus for the feasibility studies in rehabilitation research.

The findings of this thesis may have important implications especially for the development of strategies to enhance cognitive ability in HIV. The ideal “formula” for building cognitive reserve certainly requires further research. Cognitive reserve is a promising concept. It may explain why different individuals show differential rates of change in their cognitive performance. It also suggests that the manifestations of age- or disease-related cognitive impairment can be delayed by actively pursuing cognitively enriching lifestyles. However, evidence for the cognitive reserve hypothesis in HIV is mostly observational, thus the causal inferences for its protective

effect cannot be drawn. Same holds largely true for the geriatric and other clinical populations. Rigorous randomized controlled trials on the contributors of cognitive reserve are needed to strongly recommend/prescribe interventions that can benefit cognitive performance in HIV. Nevertheless, it is advisable to engage in cognitively stimulating activities as these are relatively cost-effective and are of non-invasive nature. There is likely no harm in their clinical recommendation (Stern, 2013; Scarmeas & Stern, 2004) or encouraging these activities through health promotion initiatives (Chan et al., 2018). This recommendation would also apply to people with high cognitive reserve showing no evidence of cognitive impairment as their reserve may be masking pathology (Hall et al., 2007). Clinicians should support lifestyle modifications for their patients with an emphasis on incorporating 'reserve-building' activities into their everyday lives. Although the use of computerized cognitive training is emerging as effective in improving cognition in people with HIV (Vance et al., 2019), supplementing cognitive training with recreational activities that foster cognitive reserve may prove a winning combination. Overall, these activities form the backbone of the principle of neuroplasticity (i.e., the ability of human brain to adapt according to environmental stimuli or even after experiencing neurological damage) (Wolf et al., 2006; Bosch et al., 2010) in the aging populations.

Are we further ahead in the area of cognitive reserve and HIV? Yes and no. Yes, in that while the notion of multiple factors contributing to cognitive reserve is agreed upon in the HIV and non-HIV literature, this thesis employed a method of combining these factors in a manner that was consistent with the best practices from an epidemiological perspective. The specific methodology has not been applied in the context of developing a cognitive reserve index in people with HIV and therefore makes a unique contribution to the field.

On the no side, this work focused on the socio-behavioural contributors (i.e., the lifetime

experiences) of cognitive reserve but did not consider the structural aspects of human brain that are often categorized under the passive model of brain reserve. Also, other methods including residual and functional imaging approaches (Stern et al., 2018) were not employed in this thesis. Future studies should integrate these approaches to better elucidate the concept of cognitive reserve in HIV.

Overall, this thesis contributed evidence towards the influence of cognitive reserve in bettering cognitive performance in HIV. However, the field of cognitive reserve has not converged on how to optimally operationalize it, or how to harness its power to protect cognitive abilities. Nevertheless, in an era with concerns surrounding the efficacy of current suite of drugs in protecting HIV brain (Ghosh et al., 2017), the premise of cognitive reserve seems to offer hope to those with and without cognitive impairment.

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Appendices

List of Indicators of Cognitive Reserve Captured in Positive Brain Health Now Study

1. Language:
   How many languages do you speak? _____

2. For your longest job, choose the answer that best describes your engagement for each of the job/volunteer activities listed below.

Job activities	Choices			
Job or volunteer	☐ Professional or executive (CEO, MD, university professor, lawyer, judge, surgeon, chartered accountant, engineer)	☐ Highly skilled or administrative (Nurse, electrician, plumber, IT specialist, teacher, administrative assistant)	☐ Clerical or service position (Sales representative, cashier, taxi driver, call centre operator, day labourer)	

3. Social network (first three items of Older Americans Resources and Services - Social Resources Scale)
   a. How many people do you know well enough to visit within their homes?
      - ☐ 5 or more
      - ☐ 3 to 4
      - ☐ 1 to 2
      - ☐ None
   b. About how many times in the past week did you talk to someone (friends, relatives or others) on the telephone, or by text message, or internet?
      - ☐ One or more times in a day
      - ☐ Almost every day (2 to 6 times a week)
      - ☐ Once a week
      - ☐ Less than once a week
   c. How many times during the past week did you spend some time with someone who does not live with you, that is you went to see them or they came to visit you or you went out to do things together?
      - ☐ One or more times in a day
      - ☐ Almost every day (2 to 6 times a week)
      - ☐ Once a week
      - ☐ Less than once a week

4. Education

What is the highest level of education that you have completed?

- ☐ Primary School
- ☐ High School
- ☐ CEGEP/College, technical or vocational diploma
- ☐ University Certificate, Bachelor (undergraduate education)
- ☐ University postgraduate study (MSc/PhD) or professional degree (medicine, law, …)

5. Other lifetime activities:

For each of the activities below, please choose the response that best corresponds to your level of engagement in the activity.

Activity	**Level of engagement**			
Visual, crafts or culinary arts	☐ Professional	☐ Amateur	☐ Personal enjoyment	☐ None
Music	☐ Professional performer	☐ Amateur performer	☐ Personal enjoyment	☐ None
Performance and/or literary arts	☐ Professional	☐ Amateur	☐ Personal enjoyment	☐ None
Sports	☐ Professional or national competitor	☐ Competitive amateur	☐ Personal enjoyment	☐ None
Travel	☐ 2 or more continents other than North America	☐ 1 continent other than North America	☐ Within North America	☐ Within province only

Games	☐ Competitive games (tournaments or play for money)	☐ Complex video or role playing, virtual reality (Dungeons & Dragons, Assassin's Creed)	☐ Simple card or board games	☐ None

Perceived Deficits Questionnaire (PDQ)

The following questions describe several situations in which a person may encounter problems with memory, attention or concentration. Please choose the appropriate response based on your cognitive function during the past 4 weeks. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you.

During the past **4 weeks**, how often did you...

	Never	Rarely	Sometimes	Often	Almost Always
1. Lose your train of thought when speaking?					
2. Have difficulty remembering the names of people, even the ones you have met several times?					
3. Forget what you came into the room for?					
4. Have trouble getting things organized?					
5. Have trouble concentrating on what people are saying during a conversation?					
6. Forget if you had already done something?					
7. Miss appointments and meetings you had scheduled?					
8. Have difficulty planning what to do in the day?					
9. Have trouble concentrating on things like watching a television program or reading a book?					
10. Forget what you did the night before?					

11. Forget the date unless you looked it up?					
12. Have trouble getting started, even if you had a lot of things to do?					
13. Find your mind drifting?					
14. Forget what you talked about after a telephone conversation?					
15. Forgot to do things like turn off the stove or turn on your alarm clock?					
16. Feel your mind went totally blank?					
17. Have trouble holding phone numbers in your head even for a few seconds?					
18. Forget what you did last weekend?					
19. Forget to take your medication?					
20. Have trouble making decisions?					

Stanford Presenteeism Scale (SPS)

The following sets of questions are work related questions. However, if you do not currently work, but are volunteering, you can answer the following questions based on your volunteer.

Will you be answering based on

☐	Work
☐	Volunteer work
☐	Don't work or volunteer (move to the next questionnaire)

In thinking about how your HIV has affected your ability to do your job, how often in the past 4 weeks:

	Always	Frequently	About half the time	Occasionally	Never
1.Were you able to finish hard tasks?					
2.Did you find your attention wandering?					
3.Were you able to focus on achieving work goals?					
4.Did you feel energetic enough to work?					
5.Were the stresses of your job hard to handle?					
6.Did you feel hopeless about finishing your work?					
7.Were you able to focus on finding a solution when unexpected problems arose in your work?					
8.Did you need to take breaks from your work?					
9.Were you able to work with other people on shared tasks?					
10.Were you tired because you lost sleep?					

Physical Activity Question

What best describes your physical activity level in the past 6 months?

- ☐ Vigorously active for at least 30 min, 3 times per week
- ☐ Moderately active at least 3 times per week
- ☐ Seldom active, preferring sedentary activities

The following items are about activities you might do during a typical day.
Does <u>your health now limit you</u> in these activities?
If so, how much?

<u>Activity</u>	**Yes, limited a lot**	**Yes, limited a little**	**No, not limited at all**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports			
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing **several** flights of stairs			
e. Climbing **one** flight of stairs			
f. Bending, kneeling, or stooping			
g. Walking **more than a kilometre**			
h. Walking **several blocks**			
i. Walking **one block**			
j. Bathing or dressing yourself			

Motivation

Item	Not at all	Some	A lot
1. Are you always looking for something to do?			
2. Are you interested in learning new things?			
3. Do you have plans and goals for the future?			

SF-36 Mental Health Inventory

1. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities		
b. **Accomplished less** than you would like		
c. Were limited in the **kind** of work or other activities		
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

2. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
1. Cut down the **amount of time** you spent on work or other activities		
2. **Accomplished less** than you would like		
3. Didn't do work or other activities as **carefully** as usual		

3. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

4. How much bodily pain have you had during the past 4 weeks?

- ☐ None
- ☐ Very Mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- ☐ Not at all
- ☐ A little bit
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

6. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

SF-36 Vitality

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks…**

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
Did you feel full of pep?						
Have you been a very nervous person?						
Have you felt so down in the dumps that nothing could cheer you up?						
Have you felt calm and peaceful?						
Did you have a lot of energy?						
Have you felt downhearted and blue?						
Did you feel worn out?						
Have you been a happy person?						
Did you feel tired?						