The Feasibility and Impact of a Yoga Intervention on Cognitive and Physical Performance among People Living with HIV

by

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Abstract

This dissertation consists of three main projects.

Project 1:

Cognitive impairment is common among people living with HIV (PLWH). Physical activity has emerged as a potential management strategy for cognitive impairment. The study purpose was to map the evidence on exercise and cognition in HIV. We searched 5 databases for exercise and HIV terms. Two authors independently reviewed titles/abstracts for studies addressing physical activity/exercise and cognition in PLWH. Sixteen studies were included. Two of eight interventional studies found exercise benefitted cognition. Eight non-interventional studies showed a positive relationship between physical activity and cognition. These results suggest that physical activity may improve cognition in PLWH.

Project 2:

Although compelling evidence exists about the health benefits of exercise, many PLWH are physically inactive. The study purpose was to use the Theoretical Domains Framework to investigate older PLWH's exercise barriers and facilitators. This qualitative study involved semi-structured interviews with 12 PLWH≥45 years. Data were analyzed thematically and were coded by two independent investigators. The participants had a working knowledge of exercise but were unfamiliar with specific exercise parameters. Barriers included co-morbidities, injuries, and side effects of HIV and medications. Facilitators included social support and technology. Those designing exercise interventions should incorporate strategies to address these obstacles.

Project 3:

The purpose of this pilot randomized trial was to assess the feasibility and satisfaction of a tri-weekly 12-week yoga intervention among PLWH. Other objectives included evaluating cognition, physical function, medication adherence, health-related quality of life (HRQoL), and mood among yoga participants versus controls using blinded assessors. We recruited 22 medically-stable PLWH aged≥35 years. *A priori* feasibility criteria were defined as ≥70% yoga session attendance and ≥70% of participants satisfied with the intervention using a post-participation questionnaire. Two participants withdrew from the yoga group. Mean yoga class attendance was 82% with 100% satisfaction. Intention-to-treat analyses (yoga n=11, control n=11) showed no within- or between-group differences in cognitive and physical function. The yoga group improved over time in HRQoL cognition (p=.047) with trends toward improvements in health transition *(p=.063)* and depression *(p=.055)*. This pilot study provides preliminary evidence of feasibility and benefits of yoga for PLWH.

List of Abbreviations Used

1-RM-1-repetition maximum
5STS-Five-Times Sit to Stand
6MWT-Six-Minute Walk Test
AACTG-The Adult AIDS Clinical Trial Group
ADAS-cog-Alzheimer's Disease Assessment Scale–Cognitive subscale
ADL-activities of daily living
AE-Aerobic exercise
AIDS-Acquired Immunodeficiency Syndrome
ANCOVA-analysis of covariance
ANI-asymptomatic neurocognitive impairment
B-CAM-Brief Cognitive Ability Measure
BAI-Beck Anxiety Index
BDI-Beck Depression Index
BDNF-brain-derived neurotrophic factor
BBS-Berg Balance Scale
BHIVA-British HIV Association
BRFSS-Behavioral Risk Factor Surveillance System
C3Q-Communicating Cognitive Concerns Questionnaire
CB&M-Community Balance and Mobility scale
cART-combination antiretroviral therapy
CCR5-Chemokine coreceptor
CD4+-cluster of differentiation-4
CES-D-CES-Center for Epidemiological Studies-Depression
CHAMPS-Community Healthy Activities Model Program for Seniors
CHARTER-Central Nervous System HIV Antiretroviral Therapy Effects Research
CIHRRC-Canada-International HIV and Rehabilitation Research Collaborative
CONSORT-Consolidated Standards of Reporting Trials
CRP-C-reactive protein
DNA-Deoxyribonucleic acid
EACS-European AIDS Clinical Society
EDF-Episodic Disability Framework
EQ-5D-EuroQol Five Dimensions Questionnaire)
FAHI-The Functional Assessment of HIV
HAD-HIV-associated dementia
HADS-Hospital Anxiety and Depression Scale
HAND-HIV-associated Neurocognitive Disorders
HCV-Hepatitis C
HDS-HIV dementia scale
HIV-Human Immunodeficiency Virus
HPA-hypothalamic-pituitary-adrenal
HRQoL-Health-related quality of life
HRR-heart rate reserve
IADLS-Lawton & Brody Instrumental Activities of Daily Living Scale
ICF-International Classification of Functioning, Disability and Health

IGF-1-insulin-like growth factor-1
IL-Interleuken
INSTI-Integrase strand transfer inhibitors
IPAQ-International Physical Activity Questionnaire
MACS- Multicenter AIDS Cohort Study
MCI-Mild cognitive impairment
MND-mild neurocognitive disorder
MOS-HIV-Medical Outcomes Survey-HIV
MRI-Magnetic Resonance Imaging
NNRTIs-Non-nucleoside reverse transcriptase inhibitors
NRTIs-Nucleoside reverse transcriptase inhibitors
PACE-Patient-centered Assessment and Counseling for Exercise
PEDro-Physiotherapy Evidence Database Reported Outcomes
PHQ-9-Patient Health Questionnaire-9
PA-Physical activity
PLWH-People living with HIV
POMS-profile of mood states
PRE-progressive resistive exercise
RAPA-Rapid Assessment of Physical Activity
RCT-Randomized controlled trial
RE-Resistance exercise
REB- Research Ethics Board
REDCap- Research Electronic Data Capture
RNA-Ribonucleic acid
ROC-receiver operating characteristic
SAGER-Sex and Gender Equity in Research
SCID-Structured Clinical Interview for DSM-IV
SF-36-Short Form-36
SLS-Single leg stance
SMAQ-Simplified Medication Adherence Questionnaire
SPPB-Short Physical Performance Battery
SD- standard deviation
TDF-Theoretical Domains Framework
TNF-tumour necrosis factor
TUG-timed up and go
UNAIDS-the Joint United Nations Programme on HIV/AIDS
VACS-Veterans Aging Cohort Study
VAS-visual analogue scale
VEGF-vascular endothelial growth factor
$V0_2$peak-peak oxygen consumption
$V0_2$max-maximal oxygen consumption
WHOQOL-BREF-World Health Organization Quality of Life
WIHS-Women's Interagency HIV Study

Glossary

AIDS: a CD4+ cell count below 200/mm^3 or the presence of an AIDS-defining illness

Asymptomatic: no symptoms or acute HIV symptoms

Exercise*:* planned, structured, and repetitive physical activity that aims to improve or maintain physical fitness

Gender: an individual's socially-constructed roles, behaviours, and identity

Health-related quality of life: a multi-dimensional concept that includes physical, mental, emotional, and social function domains

Lipodystrophy: fat accumulation (lipohypertrophy), fat loss (lipoatrophy), and metabolic changes from the use of antiretroviral medications

Mind-body exercise: a type of therapy, including Tai Chi, Yoga, Qigong, or dance that involves concentration, breathing, and body movement

Nadir: An individual's lowest CD4+ count

Non-linear resistance training: resistance training with varying training intensity and volume within each week

Physical activity: any bodily movement produced by skeletal muscles that results in energy expenditure

Quality of life: "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards, expectations and concerns"

Sarcopenia: reduced muscle mass and muscle function

Sex: a set of biological attributes such as someone's genetics, reproductive system, or secondary sex characteristics

Symptomatic: the presence of an HIV-related condition

Undetectable viral load/virally suppressed: defined as fewer than a prescribed number of HIV copies (usually 50) per millilitre of blood

Virologic failure: failure to suppress a person's viral load to less than a prescribed number of HIV copies per mililitre of blood

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Thesis Organization and Overview

This dissertation consists of twelve chapters, with six of the chapters written as manuscripts, four of which have been published in peer-reviewed journals and two are currently in review. Chapters 1 to 8 are reviews of the literature on topics relevant to the focus of my thesis – effects of an exercise intervention on cognition, physical functions (balance, gait, physical activity), health-related quality of life, mental health, and medication adherence in PLWH. Careful examination of the evidence was critical to inform the approach to the three main research projects we undertook as part of my doctoral studies: the scoping review described in Chapter 5, the qualitative study presented in Chapter 9, and the design and findings of the quantitative study presented in Chapter 10 and 11, respectively. Throughout this dissertation, sex and gender are discussed and evaluated, where applicable.

In terms of the content of each chapter, Chapter 1 provides an overview of HIV pathophysiology, antiretrovirals, comorbidities, and episodic disability. Chapter 2 outlines the literature on cognitive impairment, its prevalence, classification, and measurement tools. Chapter 3 is manuscript #1 "Physical Deficits among People Living with HIV: A Review of the Literature and Implications for Rehabilitation", which was published in *Physical Therapy Reviews* in December 2019. Chapter 4 summarizes the literature on quality of life, medication adherence, physical activity, and mood concerns and common measures used in HIV research. Chapter 5 consists of manuscript #2 "Exercise and Cognitive Function in People Living with HIV: A Scoping Review" which was published in *Disability and Rehabilitation* in January of 2018. Chapter 6 consists of manuscript #3, "Effects of Exercise on Cognitive Performance in Older Adults: A

Narrative Review of the Evidence, Possible Mechanisms, and Recommendations for Exercise Prescription", which outlines the available literature on the effectiveness of exercise interventions on cognitive performance among HIV-negative individuals and was submitted to *Ageing International* in February 2019. In Chapter 7, I review the evidence on the effects of exercise on physical impairments among people living with HIV. Chapter 8 summarizes the literature on exercise on health-related quality of life, medication adherence, and mental health in the HIV population. Chapter 9 is manuscript #4 "Using the Theoretical Domains Framework to Identify Barriers and Facilitators to Exercise among Older Adults Living with HIV" which is a qualitative study where we interviewed people living with HIV in the Halifax area to determine barriers and facilitators to exercise. This manuscript was published in *AIDS Care* in July of 2018. Chapter 10 is manuscript #5, "Evaluating the Feasibility and Impact of a Yoga Intervention on Cognition, Physical Function, Physical Activity, and Affective Outcomes in People Living with HIV: Protocol for a Randomized Pilot Trial", which outlines the study design, methods, outcome measures, and intervention procedures. This manuscript was published in the *JMIR Research Protocols* in May of 2019. Chapter 11 is manuscript #6, "Evaluating the Feasibility and Impact of a Yoga Intervention on Cognition, Physical Function, Physical Activity, and Affective Outcomes in People Living with HIV: A Randomized Pilot Trial", which describes the data analysis, study results and discussion, as well as implications for future work. The manuscript was submitted to *JIAPAC* in August 2019. Chapter 12 is a synthesis of the thesis that includes reflections on the overall work, research and policy implications and impact, and future research directions.

Chapter 1-Introduction

Global Epidemiology of HIV

In the year 2018, an estimated 37.9 million people worldwide were living with the Human Immunodeficiency Virus (HIV).[1] Sub-Saharan Africa has the highest percentage of people living with HIV (PLWH) with 53% of the global prevalence.[2] The global incidence of HIV has decreased from 3.4 million new infections in 1996 to 1.8 million in 2017 while the rate of new infections is increasing in eastern Europe and central Asia.[2] The most recent estimates indicate that 23.3 million people worldwide have access to antiretroviral treatment.[1] Despite improved access to treatment, 770,000 people died in 2018 as a result of acquired immunodeficiency syndrome (AIDS).[1]

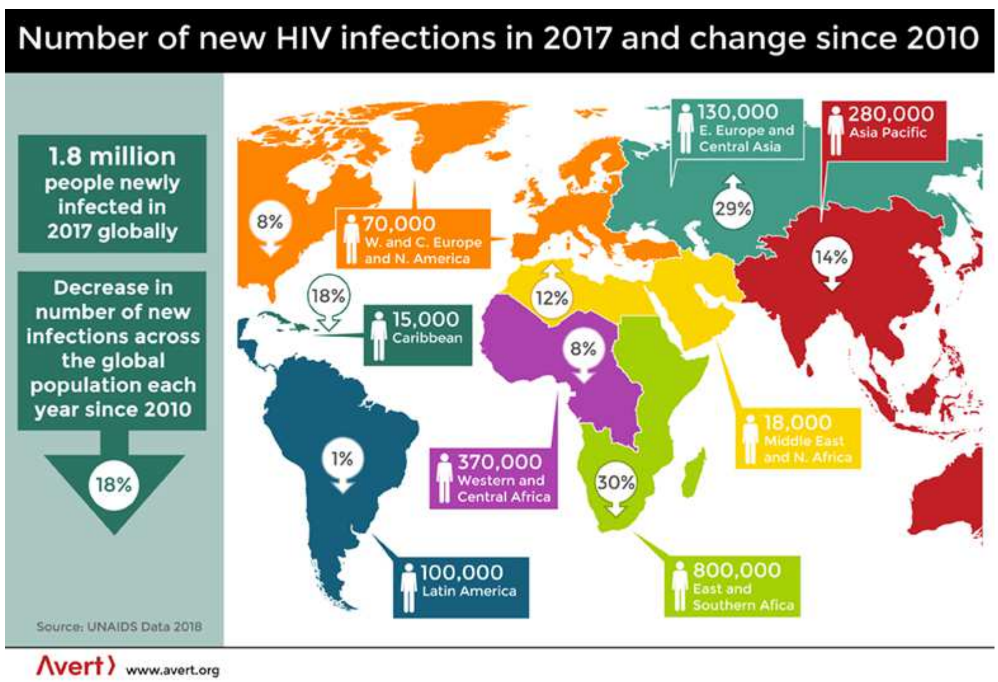

Figure 1: Global HIV infections

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Global HIV Demographics

Women living with HIV represented 48% of PLWH globally in the year 2016.[4] Young women aged 15-24 are particularly at risk of contracting HIV, with 7,000 new infections occurring each week among these individuals.[5] In sub-Saharan Africa, three quarters of new HIV infections are among girls, and young women are twice as likely to be infected than young men.[6] Global HIV rates are also disproportionately higher among younger individuals, men who have sex with men, transgender individuals, people who use drugs, and sex workers.[7]

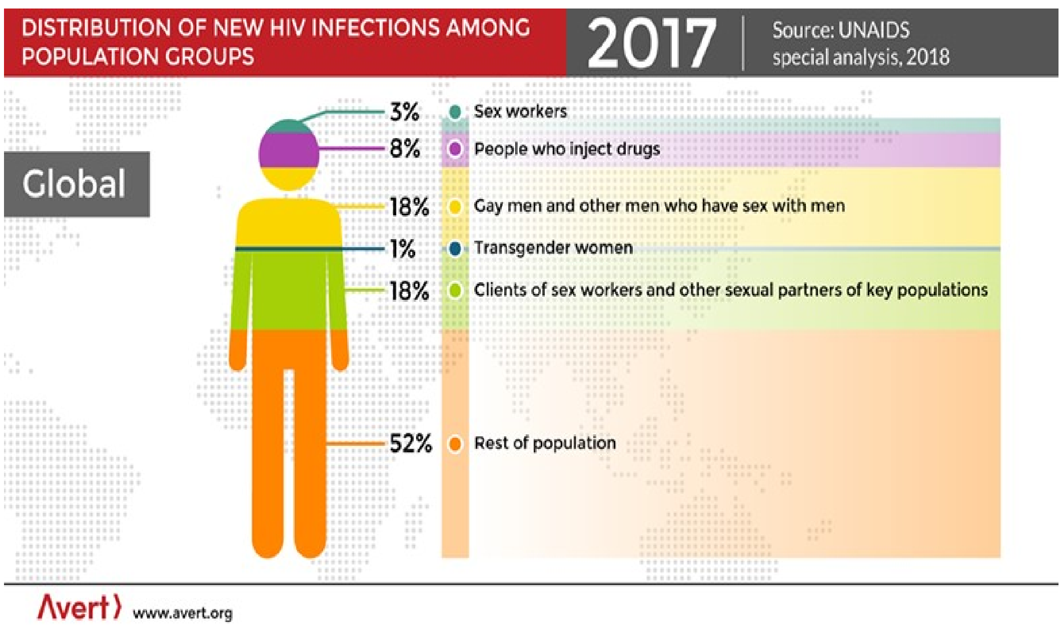

Figure 2: Distribution of new HIV infections
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HIV Prevalence and Incidence in Canada

An estimated 63,110 Canadians were living with HIV at the end of 2016, with women making up approximately 23% of all PLWH in Canada.[8] Meanwhile, the incidence of new HIV infections overall has increased slightly in Canada since 2014.[8] Men who have sex with men represent the largest share of new HIV infections (52.5%), while 33.2% of new infections are attributed to heterosexual sex, and 11.3% are attributed to injection drug use in Canada.[8] In 2017, 75% of new HIV infections in Canada were among men and 25% were among women.[9] HIV infection is currently overrepresented among Indigenous people, who account for 11.3% of new infections despite only making up 4.9% of the Canadian population.[8] Similarly, individuals from HIV-endemic countries (2.5% of the Canadian population in 2011) represented 13.6% of new infections in the year 2016.[8]

Modes of Transmission

There are multiple HIV transmission modes: sexual intercourse, intravenous needles, mother-to-child (also known as vertical transmission during pregnancy, childbirth, or breastfeeding) and via blood products.[10] The largest risk factor for HIV transmission is an individual's viral load (the number of copies of HIV per millilitre of blood).[11] Other risk factors that increase HIV transmission risk include multiple sexual partners and concurrent sexual partnerships.[12,13]

HIV Pathophysiology and Classification

HIV is a retrovirus that primarily affects the cluster of differentiation-4 (CD4+) cells, monocytes, macrophages, and dendritic cells of the immune system.[14] The virus enters the immune cells and directs them to produce a viral enzyme, reverse transcriptase, which converts viral ribonucleic acid (RNA) into deoxyribonucleic acid (DNA).[15] The result of untreated HIV is immune system destruction, with a progressive reduction in CD4+ and CD8+ cells. There is also elevated pro-inflammatory cytokine production which exacerbates tissue damage, particularly in the gastrointestinal tract, allowing microbes to enter the circulatory system, thereby increasing inflammation.[16] In the absence of combination antiretroviral therapy (cART), there are three stages of HIV infection: acute HIV infection, clinical latency, and AIDS.[17]

Acute HIV Infection

Following the initial transmission of the virus, there is a dramatic increase in HIV replication, inflammatory cytokines, and chemokines during the first 6-12 weeks.[14] Two to four weeks following viral incubation, many individuals experience flu-like symptoms including fever, sore throat, rash, muscle aches, and headache. During this stage, the virus is replicating rapidly and therefore, individuals are highly infectious.[18] At the same time, most individuals are not aware that they have been infected, further increasing the risk of transmission.[18]

Clinical Latency

During this stage of infection, which lasts up to several years, the virus continues to replicate slowly without the presence of symptoms. At the end of the clinical latency phase, the viral load begins to increase while the CD4+ count decreases, which signifies progression to AIDS.[19]

AIDS

An individual progresses to the third stage when the immune system deteriorates and becomes susceptible to opportunistic infections. The clinical definition of AIDS as determined by the Centers for Disease Control and Prevention is a CD4+ cell count below 200 cells per cubic millimetre or the presence of an AIDS-defining illness.[19] These opportunistic illnesses include certain infections and cancers and are said to be AIDS-defining based on the type of illness, location in body, and the duration of the illness.[19]

Clinical Classification

The Centers for Disease Control and Prevention also classifies PLWH in terms of their clinical presentation.[20] Category A (asymptomatic) includes individuals with acute HIV infection or persistent generalized lymphadenopathy.[20] Category B (symptomatic) includes PLWH with conditions attributed to HIV, such as thrush or constitutional symptoms such as fever or diarrhea.[20] Category C (AIDS) consists of individuals with AIDS-identifying conditions.[20] Many studies use this classification system to describe participants; therefore, we will use these terms throughout this dissertation where applicable.

Antiretroviral Therapy

Since 1996, the advent of cART has resulted in dramatic improvements in health and life expectancy among PLWH.[21] cART regimens typically consist of three medications from at least two different drug classes and are recommended for all PLWH with detectable viral loads, irrespective of CD4+ count.[22] The initiation of cART is also recommended for PLWH with undetectable viral loads (typically defined as fewer than 50 HIV copies per millilitre of blood[23]) but have a CD4+ count that is declining.[24] There are six classes of drugs, including, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion inhibitors, chemokine coreceptor (CCR5) antagonists, and integrase strand transfer inhibitors (INSTI).[25] Each drug class targets a different phase of the virus replication cycle.[25] Mutations occur each time the virus replicates; therefore, multiple drugs are needed to prevent mutations.[25]

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set an ambitious target known as the 90-90-90 goal, whereby 90% of PLWH would know their status, 90% would initiate cART, and 90% would achieve virological suppression by the year 2020.[26] In 2018, 79% of PLWH worldwide knew their status and 62% were accessing treatment.[1] Although more PLWH are accessing treatment, only 53% of PLWH worldwide have undetectable viral loads[1] and some national HIV programs have determined that the 90-90-90 targets are unrealistic.[23]

Adherence to cART

Numerous factors are thought to influence cART adherence. Despite improvements in cART tolerance, PLWH commonly report side effects such as nausea, diarrhea, lipodystrophy, dermatological problems, hepatotoxicity, and elevated triglycerides.[27] cART side effects are consistently cited as a reason for non-adherence;[28] some evidence indicates that side effects from cART medications account for 10-15% of treatment discontinuations.[29] Individuals who use alcohol, intravenous drugs, and other substances tend to have decreased cART adherence and are at an increased risk of virologic failure (defined as the failure to suppress a person's viral load to less than 200 HIV copies per mililitre of blood in this study).[30–32] Homelessness and mental health disorders such as depression are also associated with poor cART adherence among PLWH.[31,33,34]

Comorbidities

The combination of HIV infection and cART use has increased the risk of non-AIDS comorbidities such as cardiovascular disease, stroke, diabetes, and metabolic syndrome.[35] Cardiovascular and metabolic risk factors commonly observed among

PLWH include dyslipidemia, insulin resistance, obesity, subcutaneous lipoatrophy, and bone demineralization.[36] Hepatitis C (HCV) and HIV-coinfected individuals have a higher incidence of metabolic syndrome and cardiovascular disease, which may also increase mortality risk.[37] PLWH are at a higher risk of developing certain cancers relative to the general population, due to immunosuppression and viral co-infections.[38] Approximately 2.4-10% of PLWH have impaired kidney function depending on participants' social and demographic characteristics.[39] HIV-associated nephropathy and cART-related nephrotoxicity are common kidney conditions observed in this population. Despite the widespread use of cART, PLWH are also experiencing high rates of fatigue (43%), insomnia (35%), anxiety (34%), and pain (31%).[40]

Episodic Disability

HIV, as with other chronic illnesses such as migraines, chronic fatigue syndrome, and chronic pain, can be described as episodic in nature. Episodic disability has been characterized by O'Brien and colleagues as "'unpredictable periods of wellness and illness".[41] PLWH tend to experience day-to-day fluctuations in physical, cognitive, mental, emotional, functional, and social health dimensions.[42] To describe and explore the experiences of PLWH with episodic disability, O'Brien and colleagues developed the Episodic Disability Framework (EDF).[42] It is the first known conceptual framework of disability developed from the perspective of PLWH.[43] The EDF breaks down episodic disability into its four components: Symptoms and impairments, challenges with day-to-day activities, challenges to social inclusion, and uncertainty.[43] These four dimensions are interconnected in that each dimension is associated with the other three dimensions.[43] A large cross-sectional study conducted in Canada revealed that uncertainty is a key aspect of HIV-associated disability that predicts both mental-emotional health and social inclusion among PLWH.[44] In addition, the EDF includes intrinsic factors such as living strategies and personal attributes as well as extrinsic factors such as social support and stigma can exacerbate or alleviate one's experience of disability.[43]

Chapter 2- HIV-Associated Cognitive Impairments and Mechanisms

Background

Despite the beneficial effects of cART, cognitive impairment is common among PLWH. These deficits are characterized by difficulties in executive function, language, memory, processing speed, attention, and sensory and motor function.[45,46] Approximately 15-69% of PLWH on cART have some form of cognitive impairment.[38-42] A study by Simioni and colleagues of 200 PLWH (of whom 72% were male) with undetectable viral loads estimated the prevalence of cognitive impairment among PLWH to be as high as 69% (50% with asymptomatic neurocognitive impairment, 17% mild neurocognitive impairment, and 2% HIV-associated dementia).[48] In contrast, Heaton and colleagues determined that 52% of 1,555 majority-male PLWH had cognitive impairment, but the mean age of the participants was lower and their sample had fewer female participants than the abovementioned study by Simioni et al.[47]

Cognitive impairment rates are expected to increase over time as PLWH live longer; by the year 2030, the number of individuals with HIV-associated cognitive impairment will increase 5- to 10-fold.[52] At the same time, cognitive decline is persisting despite cART treatment. A large cohort study of 701 mostly-male PLWH determined that 15.8% demonstrated evidence of cognitive decline in at least one of fifteen neuropsychological tests over three years.[53] Another study using a subset of participants from the same cohort (80% of whom were male) identified higher but similar rates of cognitive decline (22.7%) over 35 months among PLWH using different methods of calculating change.[54]

Cognitive impairment can result in lower quality of life, increased unemployment, and reduced life expectancy among PLWH.[55–57] Of particular importance, cognitive impairment is a potent predictor of cART adherence among older PLWH.[58] Executive function, motor function, and processing speed are strongly associated with medication adherence among older PLWH but not younger PLWH, as determined by a cohort study of mostly male 431 PLWH.[58]

Classification

Before 1991, HIV-associated dementia (HAD) was the only known type of neurocognitive impairment described among PLWH.[59] In 1991, the American Academy of Neurology added minor cognitive motor disorder to the classification in order to describe cognitive impairment in this population.[60] Currently, the most common method used to classify HIV-associated neurocognitive disorders (HAND) is the Frascati criteria, which was developed in 2007 and specifies the three stages of cognitive impairment in people living with HIV: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HAD.[47] It is important to note that a HAND diagnosis under the Frascati classification system cannot be made if an individual is diagnosed with comorbidities known to influence central nervous system function, such as neurological opportunistic infections.[46]

An ANI diagnosis is made when neurocognitive scores are more than one standard deviation away from normative test scores in at least two out of seven cognitive domains, but the individual does not report cognitive symptoms.[45,46] The same clinical criteria are used to diagnose MND, but the individual has impairments in everyday functioning[45] such as difficulties with complex task performance, reading, and attention.[61] A HAD diagnosis is made when deficits are observed in at least two cognitive domains, the scores are two or more standard deviations away from normative test scores, and the impairments have a significant impact on everyday function.[45] This stage is characterized by severe memory and executive function deficits.[59]

To determine which HAND subcategory should be assigned, clinicians and researchers must assess the severity of objective cognitive impairment, the extent to which the cognitive impairment interferes with activities of daily living, and whether the patient attributes changes in functional performance to cognitive impairment.[62] Differentiating between the HAND subcategories can be important clinically both for determining how cognitive impairment affects everyday functioning and to help the clinician determine the patient's cognitive trajectory.

Epidemiology

Prior to the advent of cART in the year 1996, HAD occurred in 50% of PLWH before death.[63] In the cART era, the profile of cognitive impairment has shifted toward milder forms with a 40–50% decrease in HAD rates,[64] and this transition catalyzed the addition of ANI into the classification system.[46] According to Heaton et al. (2010), HAD rates have declined to include only 2.4% of PLWH,[47] but milder forms of cognitive impairment are becoming more prevalent,[65] with most PLWH presenting with ANI and MND (32.7% and 11.7% prevalence, respectively).[47] Importantly, PLWH with asymptomatic cognitive impairment have double the risk of developing symptomatic cognitive impairment relative to PLWH without cognitive impairment.[65]

Clinical Presentation

In the cART era, the clinical presentation of HIV-associated cognitive impairment has expanded from primarily subcortical deficits affecting motor and processing speed tasks to the addition of cortical impairments in executive function, memory, and learning domains.[66,67] Mood and behaviour changes are also evident in this population, including apathy, emotional changes, and a loss of spontaneity.[48] Of note, clinical and neuropsychological profiles can be heterogeneous, with variation in both cognitive domains and diagnostic methods.[68]

Magnetic resonance imaging (MRI) studies conducted with individuals with HAD have determined that there are diffuse white matter changes with associated cerebral atrophy, enlarged sulci and lateral ventricles.[69] Cortical atrophy begins in the frontal lobes,[70] occurring progressively in both subcortical and cortical regions as HIV progresses.[71,72] These changes in brain structure are associated with cognitive performance; there is a strong relationship between global brain atrophy, signal changes in the basal ganglia, and cognitive impairment among PLWH.[73] A description of the cognitive domains commonly affected by HIV infection will follow.

Attention and Concentration

The most common cognitive deficit observed among PLWH is in attention performance,[74] which typically begins with difficulties in simple attention tasks and becomes more evident with divided attention,[75] complex attention,[76] orientation,[77] and visual search and discrimination tasks.[78] These impairments are less evident during the early stages of HIV and tend to appear in the later stages of HIV progression.[79] Attention deficits do not appear to lessen with cART treatment; a longitudinal study determined that 63% of male PLWH on long-term treatment followed for 8 years had persistent attention impairments.[80]

Memory

The most frequently affected aspects of memory among PLWH are episodic and prospective memory. Episodic memory impairments manifest in difficulties with both memory encoding and retrieval,[81] presenting with deficits with impaired immediate and delayed recall.[82] Such deficits are observed in 40-60% of PLWH[76] and tend to be mild to moderate in severity, but like attention, increase in severity among those with advanced HIV.[79] Prospective memory deficits are commonly observed among PLWH and predict difficulties with instrumental activities of daily living (ADL) performance[83] and medication non-adherence.[84] Subtle changes in working memory have been observed,[59,74] with PLWH demonstrating impairments on visual and verbal working memory tasks.[85,86] Working memory and attention deficits are among the strongest predictors of self-reported cognitive concerns.[87]

Language

Language deficits are typically mild in the HIV population. Verbal fluency impairments are the most common and are observed in 40% of PLWH.[88] Among PLWH, basic receptive and expressive language performance are normally preserved;[89] however, among individuals who have progressed to AIDS, mild difficulties with complex expressive language may become apparent.[79] A meta-analysis of 37 studies concluded that verbal fluency impairments are mild among PLWH but may worsen in advanced stages of HIV infection.[90]

Executive Function

Executive function tasks involve advanced cognitive processes such as reasoning, decision-making, problem solving, and planning. These abilities are strongly associated with difficulties with everyday tasks among PLWH.[61] In the later stages of HIV infection, executive function impairments become more prevalent.[79] Abstraction and problem-solving, response inhibition, set shifting, and planning difficulties are commonly observed among PLWH.[63,74,76,79]

Information Processing

Slowed information processing is a key neurological feature of AIDS.[91] Information processing is closely associated with other cognitive domains; as a result, impairments in this area can lead to deficits in other cognitive domains.[91,92] A cART-era study of 186 PLWH (65% of whom were male) determined that processing speed explained 71% of the variance in learning, 74% of the variance in memory, and 77% of the variance in executive function in their sample.[92] The authors concluded that the diffuse impairments in cognitive performance observed in PLWH may be explained in part by deficits in processing speed.[92]

Motor Skills

Motor slowing is frequently observed during gait speed[93] and fine motor tests among PLWH.[76,94] PLWH treated with cART continue to experience psychomotor problems, especially in those with advanced HIV.[79,95] It is currently unclear whether cART can improve motor performance. A longitudinal study by Suarez and colleagues (2001) followed 53 PLWH (86% of whom were male) treated with cART and concluded that there is a positive association between cART duration and cognitive performance.[96] Of note, the investigators noted an improvement in psychomotor performance using the Purdue pegboard test during the study period (12.3 ± 8.3 months).[96] Conversely, a recent longitudinal study by Elicer and colleagues (2018) of 164 mostly-female (59%) PLWH (88% of whom were treated with cART) evaluated a subset of 78 PLWH with data from 4 years prior or more and demonstrated that cognitive performance remained stable but motor function declined over time.[97] The discrepancy in results between the two aforementioned studies could be explained by differences in age (mean age in the study by Suarez and colleagues = 38, Elicer and colleagues = 52) which may indicate that older PLWH are more likely to decline in motor function than younger individuals.

Visuoperceptual Skills

Similar to working memory and language impairments, subtle deficits in visuoperceptual performance are present among PLWH.[91] HIV serostatus is related to worsening performance on a mental 3-dimentional object rotation task, indicating posterior parietal cortex and fronto-striato-parietal neural network dysfunction, according to a study of 34 mostly-male PLWH and HIV-negative participants.[98] PLWH also demonstrate impairments in global visual processing[99] and perceptual span performance,[100] which may increase the risk of accidents.[101]

Risk Factors for Cognitive Impairment

There are many risk factors for developing HIV-associated cognitive dysfunction, including the direct effect of HIV on the brain, aging, localized and systemic inflammation, opportunistic brain infections, comorbidities, mood disorders and insomnia, lifestyle factors, cART use, and sex and gender differences. A discussion of relevant risk factors follows.

Viral Factors

Immediately following HIV infection, the virus enters the brain via myeloid and lymphoid cells,[102] which can contribute to neurological symptoms. HIV is able to cross the blood-brain barrier, where it becomes established in the perivascular macrophages, microglia, and astrocytes to serve as life-long reservoirs.[103] Meanwhile, viral gene products such as transactivator of transcription (tat) and envelope glycoprotein 120 (gp120) promote apoptosis and neuron damage,[104] and reduce brain-derived neurotrophic factor (BDNF) levels.[105] The largest source of damage to neurons is caused by HIV-infected glial cells, which contribute to widespread inflammatory processes.[106]

Certain HIV markers have been used to estimate immune activation in the central nervous system. Previously, the CD4+ nadir (lowest CD4+ count) was thought to predict neurological disease in PLWH.[107] There was also preliminary evidence to indicate that CD4+ nadir was associated with HAD diagnosis.[108] However, newer evidence suggests that immune function is not related to cognitive performance; Simioni and colleagues failed to find any differences in immune function markers (including viral load, CD4+ count, and CD4+ nadir) between PLWH with and without cognitive impairment.[48] These findings indicate that HIV-associated cognitive impairment persists despite effective cART treatment.

Aging

The combined and potential synergistic effect of age and HIV on brain structure and function among PLWH has become a concern over the past decade.[109–111] As PLWH age, the prevalence of cognitive impairment increases substantially.[112] Older PLWH have triple the risk of developing cognitive impairment compared to younger PLWH.[113] There is evidence that PLWH experience an accentuated aging process; Vance and colleagues observed in their study of 162 PLWH (of whom 57% were male) and HIV-negative participants that older PLWH performed worse on 8 of 9 neuropsychological and functional tests than both younger PLWH and HIV-negative individuals.[114] Additionally, PLWH over the age of 50 have double the risk of developing HAD than younger PLWH.[115] Since HIV-associated cognitive impairment is expected to increase in the next decade,[116] and new infections are on the rise among older adults;[117] this has become a public health concern.[118]

Inflammation

Inflammation appears to contribute to cognitive impairment among PLWH.[119] Following HIV infection, the blood-brain barrier becomes more permeable,[63] which is associated with elevated immune activation.[64] Despite effective cART treatment, macrophages and monocyte inflammation are present in the brain.[122] Macrophages infiltrate the brain and stimulate the release of pro-inflammatory cytokines and chemokines,[123] which can contribute to neurodegeneration and diminished synaptic function.[124] As glial cells are damaged, neutoxic cytokines and quinolic acid are released, which contribute to neuroinflammation and oxidative stress, further compromising neurons and other glial cells.[125] Leaky gut syndrome also leads to systemic and neural inflammation, allowing toxins to enter the circulatory system.[126]

Comorbidities

Comorbidities, including HCV coinfection, cardiovascular disease risk factors, diabetes, and obesity are each associated with cognitive impairment among PLWH, especially among older PLWH.[127] A Central Nervous System HIV Antiretroviral Therapy Effects Research (CHARTER) study of 1555 mostly-male PLWH determined that cognitive impairment was present in 52% of participants.[47] Among participants with severe neurological and psychiatric conditions, however, cognitive deficits were observed in 83% of these individuals.[47] Cardiovascular risk factors are also strong predictors of cognitive deficits among PLWH. A cross-sectional study of 292 participants (42% of whom were female) concluded that PLWH with cardiovascular disease had 6.2-fold higher odds of cognitive impairment at baseline.[128] Comorbidities such as cardiovascular disease, diabetes mellitus, and abdominal obesity are also associated with lower cognitive functioning among PLWH with suppressed viremia.[129]

Hepatitis C (HCV) infection is independently associated with cognitive impairment,[130] and individuals with HIV and HCV co-infection demonstrate larger impairments than those who are HIV mono-infected, according to a systematic review and meta-analysis of 24 prospective studies.[131] A study of 45 HCV or HIV mono-infected and 20 co-infected participants determined that cognitive performance among mono-infected and co-infected PLWH on cART treatment was similar, but larger cognitive deficits were observed among untreated co-infected participants than mono-infected participants.[132]

This evidence indicates that cART treatment may reduce the negative effects of HCV on cognitive performance among PLWH.[132]

Central nervous system opportunistic infections including neurotoxoplasmosis, progressive multifocal leukoencephalopathy, primary central nervous system lymphoma, and cryptococcal encephalitis occur primarily in individuals with AIDS.[64] With the introduction of cART, neurological opportunistic infections have decreased significantly.[133] Despite this decrease in opportunistic infections, they continue to have a negative impact on cognitive performance. A prospective study concluded that opportunistic infections were associated with cognitive impairment among PLWH, and neurotoxoplasmosis contributed to the largest deterioration in cognitive performance.[134]

Mood Disorders and Insomnia

A large cross-sectional study (n = 2,863, 62% of whom were male) determined that 33% of PLWH identified symptoms of anxiety and 15.7% identified depression symptoms.[135] It is unclear how much depression contributes to cognitive deficits; a cross-sectional study conducted with HIV-negative young adults found evidence of a modest association between depressive symptoms and mild cognitive difficulties.[136,137] Nonetheless, self-identified cognitive challenges among PLWH have been associated with depressive symptoms[138] and a meta-analysis determined that depression severity among HIV-negative individuals is associated with cognitive deficits.[139] A study conducted by Cysique et al. concluded that incident major depression did not affect cognitive performance but lifetime major depressive disorder was associated with greater cognitive complaints among male ambulatory PLWH.[140] This evidence supports the notion that depression severity or duration could serve as cognitive modifiers among PLWH.

Approximately 29-97% of PLWH experience sleep disturbances, according to a review of 19 studies involving predominantly male PLWH.[141] A cross-sectional study determined that 73% of 115 PLWH (69% of whom were male) had symptoms of insomnia.[142] These sleep disturbances may have an impact on cognitive performance; a cross-sectional study of 116 mostly male PLWH and HIV-negative individuals determined that poor sleep health was associated with lower cognitive performance in both groups, particularly learning and memory.[143] Compared with PLWH with positive sleep health, PLWH with poor sleep health performed worse on learning and memory tasks.[143]

Lifestyle Factors

Alcohol and drug use and physical inactivity use are known risk factors for developing cognitive impairment among PLWH. The combination of HIV and alcohol dependence may have a synergistic effect on verbal reasoning, auditory processing, and reaction time.[144] The authors of a study of 50 PLWH and 30 HIV-negative male individuals with and without a history of alcohol dependence determined that PLWH with a history of alcohol use had significantly lower cognitive performance compared to PLWH without a history of alcohol use, while this effect was not observed among HIV-negative men.[144] Drug use is common in this population; a large cohort study of 3,413 PLWH determined that 24% of participants used marijuana, 9% used amphetamines, 9% used crack cocaine use, 3.8% used injection drugs, 2% used opiates, and 10.3% used multiple drugs.[145] Intravenous drug use contributes to cognitive impairment by promoting replication of the HIV virus and weakening the immune system.[146] Chronic cocaine use may also promote viral replication and apoptosis while increasing the permeability of the blood–brain barrier.[147]

Many PLWH are not achieving recommended levels of physical activity.[148] A meta-analysis of 24 studies determined that only 51% of PLWH achieved the physical activity recommendations of 150 minutes of moderate intensity physical activity per week.[149] Evidence is mounting (8 cross-sectional studies of 1,318 PLWH) to indicate that lower levels of physical activity among PLWH are associated with worse cognitive performance.[150–157]

cART Use

cART is the accepted treatment for HIV-associated cognitive impairment. A meta-analysis of 23 studies determined that cART initiation was associated with small but significant improvements in attention, (mean cohen's $d = .17$) executive function (mean cohen's $d = .18$), and motor function (mean cohen's $d = .24$).[158] However, cART use is not associated with improvements in language, verbal memory, visual memory, or visuospatial performance, meaning that impairments in these domains tend to persist despite treatment.[158] While the evidence indicates that cART reduces cognitive impairment severity among PLWH,[159] some cART medications may be neurotoxic,[159,160] and may contribute to small vessel disease in the brain.[161] Hepatotoxicity, pancreas failure, cardiomyopathy, and other cardiovascular diseases[162] may also develop as a result of cART use.[163]

Sex and Gender Differences

Some evidence exists to support the presence of sex and gender differences in cognitive impairment among PLWH. According to a study that evaluated longitudinal data from two cohorts (the Women's Interagency HIV Study [WIHS] and Multicenter AIDS Cohort Study [MACS]), female PLWH demonstrate higher rates of cognitive impairment than men in areas such as attention, processing speed, executive function, and fine motor performance.[164] According to their aforementioned study, Simioni and colleagues also determined that participants with cognitive impairment were more likely to be female compared to those without cognitive impairment.[48] There is evidence of cognitive differences at a younger age: a study of 250 younger PLWH and 72 HIV-negative controls (mean age = 23) determined that HIV did not have an effect on most cognitive domains, but there was a significant interaction between HIV status, sex, and psychomotor performance, and female PLWH had worse psychomotor performance than female controls.[165] This research indicates that HIV may have a more potent effect on motor function in women. The effect of sex and gender on cognitive performance should be evaluated further in this population.

Cognitive Measures

Neuropsychological Assessment

A HAND diagnosis is made using a neuropsychological battery assessing at least five cognitive domains commonly affected by HIV.[46] Testing of the following cognitive domains is recommended with at least two measures per cognitive domain: verbal fluency/language; attention/working memory; abstraction/executive function; memory (learning and immediate and delayed recall); information processing speed; sensory/perceptual function; and motor performance.[46] Cognitive batteries can be time consuming (they take approximately 2-4 hours to administer), and must be administered and interpreted by a trained neuropsychologist.[166] Cognitive performance batteries have been validated with large HIV cohort studies, and have been shown to have excellent validity and reliability.[167] It is important to note that fluctuations in cognitive performance occur among PLWH and some neuropsychological tests are susceptible to practice effects. To mitigate practice effects, many cognitive tests have alternative versions.[46]

Table 1: Common neuropsychological battery tests

Test	Abbreviation	Admin Time (min)	*T*-score Mean (SD)	*Materials*	*Approximate Cost*	*Public domain vs. Copyrighted*
Verbal Fluency						
Letter Fluency	FAS	6	49.87 (9.66)	Paper score sheet, stopwatch	$0	Public domain
Animal Fluency	ANIMF	2	49.54 (9.54)	Paper score sheet, stopwatch	$0	Public domain
Action Fluency	ACTF	2	48.07 (10.32)	Paper score sheet, stopwatch	$0	Public domain
Abstraction/Executive Functioning						
Wisconsin Card Sorting Test (WCST) (Total Errors)	WCST	15	53.18 (11.50)	Computer program OR stimulus cards+ paper score sheet	$820.00 (computer version) OR $375.00 (paper version)	Copyrighted
Trail Making Test - B	TMTB	5	50.51 (10.51)	Paper stimuli, pencil, stopwatch	$0	Public domain
Stroop Incongruent Test	STRPINC	1	49.98 (10.87)	Paper stimuli, stopwatch	$40.00–$149.00 (Stroop kit)	Copyrighted
Speed of Information Processing						
WAIS-III Symbol Search	SYMS	3	54.53 (9.47)	Paper stimuli, score sheet, pencil, stopwatch	$415.00 (WAIS-III kit)	Copyrighted
WAIS-III Digit Symbol	DSYM	3	51.15 (9.77)	Paper stimuli, score sheet, pencil, stopwatch	$415.00 (WAIS-III kit)	Copyrighted
Trail Making Test - A	TMTA	1	48.64 (9.65)	Paper stimuli, pencil, stopwatch	$0	Public domain
Stroop Color Test	STRPCOL	1	49.79 (11.53)	Paper stimuli, stopwatch	$40.00–$149.00 (Stroop kit)	Copyrighted
Attention/Working Memory						
Paced Auditory Serial Addition Test - 50	PASAT	5	46.10 (10.06)	Audio recording, paper score sheet	$0	Public domain
WAIS-III Digit Span	DSPAN	5	49.82 (9.65)	Paper score sheet	$415.00 (WAIS-III kit)	Copyrighted
Learning						
Brief Visuospatial Memory Test - Revised (Learning Trials)	BVMTR-LRN	10	51.82 (8.98)	Stimulus book, blank paper, pencil	$336.00 (BVMT-R kit)	Copyrighted
Hopkins Verbal Learning Test – Revised (Learning Trials)	HVLTR-LRN	10	44.09 (9.50)	Paper score sheet	$326.00 (HVLT-R kit)	Copyrighted
Recall						
Brief Visuospatial Memory Test - Revised (Total Recall)	BVMTR-RCL	30	50.38 (11.11)	Blank paper, pencil	$336.00 (BVMT-R kit)	Copyrighted
Hopkins Verbal Learning Test – Revised (Total Recall)	HVLTR-RCL	30	45.80 (9.57)	Paper score sheet	$326.00 (HVLT-R kit)	Copyrighted
Motor Speed and Dexterity						
Grooved Pegboard - dominant hand	PD	3	45.05 (9.20)	Pegboard, pegs, stopwatch	$73–$218	Copyrighted
Grooved Pegboard - non-dominant hand	PND	3	44.11 (9.52)	Pegboard, pegs, stopwatch	$73–$218	Copyrighted

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Screening Tools

Given that neuropsychological testing is time-consuming and expensive, researchers are investigating abbreviated tests and screening tools to identify cognitive impairment among PLWH.[168–170] Recently, computerized tests such as the CogState[171] and abbreviated tests such as the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog)[172] and Brief Cognitive Ability Measure (B-CAM)[170,173,174] have been used to assess cognitive function among PLWH,[175,176] and may have some clinical utility. The Cogstate has good construct validity among PLWH and correlates well with traditional neuropsychological batteries.[171,175,177] The ADAS-cog has been used in a cross-over randomized trial to determine the effectiveness of a drug (Rivastigmine) in treating HAND among PLWH.[176] To date, however, the psychometric properties of the ADAS-cog have not been evaluated in this population. The B-CAM is an abbreviated computer-based cognitive measure developed using Rasch analysis specifically for use in PLWH.[170,173,174]

There is a need for fast, simple, and validated screening instruments to detect mild cognitive impairment among PLWH. The 2013 British HIV Association (BHIVA) Standards of Care for People Living with HIV[178] and the Mind Exchange Working Group[179] recommend routine screening for cognitive impairment among PLWH. The BHIVA guidelines recommend asking questions such as, "Have you noticed any problems with your mood or memory over the past year?" and, if the response is affirmative, moving onto validated questionnaires and cognitive tests.[178] The European AIDS Clinical Society (EACS) guidelines recommend screening for cognitive impairment only in symptomatic individuals or those without confounding conditions such as depression or opportunistic infections.[180] They recommend cognitive screening when the HIV diagnosis is made and prior to cART initiation and have developed an algorithm for clinicians to follow for those with cognitive symptoms.[180] The Mind Exchange Working Group[179] recommends screening for all patients with HIV, regardless of cognitive symptoms, and say there is limited evidence to suggest that only symptomatic patients should be screened.[91,138,181]

Some authors have cautioned against using screening tools as a substitute for a complete neuropsychological evaluation.[182] Other authors do not recommended routine screening for asymptomatic cognitive dysfunction among PLWH due to concerns regarding lack of efficacious treatment options, over-diagnosis of cognitive impairment, and the potential anxiety elicited by the diagnosis.[183] Contrary to the previous statement regarding a lack of treatment options, however, there is strong evidence that exercise is an effective method of improving cognitive performance among HIV-negative older adults with mild cognitive impairment and dementia.[184,185] Therefore, PLWH, particularly those who identify cognitive concerns, should be offered neuropsychological testing and education on exercise prescription as part of routine care.

Self-Reported Cognition Measures

Self-report measures of cognitive difficulties such as the modified Lawton & Brody Instrumental Activities of Daily Living Scale (IADLS) and the Patient's Assessment of Own Functioning Inventory have been shown to be significantly associated with objective measures of neuropsychological performance among PLWH.[138,186] Another self-reported questionnaire, the Communicating Cognitive Concerns Questionnaire (C3Q) was developed with PLWH to estimate the presence and frequency of cognitive difficulties in this population.[187] Prior to cART, the HIV-dementia scale (HDS) was used to identify HAD with 80% sensitivity (with a cut-off score of 10 or less out of 16).[188] A cART-era study identified a cut-off score of 14 points or less on the HDS using a receiver operating characteristic curve, providing a positive predictive value of cognitive impairment of 92% among those with self-reported complaints and 82% among those without complaints.[48] Other studies have found that the HDS is not sensitive to mild cognitive impairment, as evidenced by a study of 46 PLWH (87% male) on cART who underwent neuropsychological evaluation.[189] Another study conducted by Underwood and colleagues found only weak associations between cognitive impairment and self-reported physical and cognitive outcomes in their sample of 387 (81% male) PLWH.[190] The authors attributed this finding to the contemporary, mild, and asymptomatic presentation of cognitive impairment among PLWH in the cART era.[190]

Laverick and colleagues (2017) found an association between lower cognitive function and both an increasing frequency of self-reported cognitive difficulties as well as a self-reported decline in ADLs in their sample of 448 PLWH (84% male).[186] However, they also determined that self-reported questionnaires demonstrated poor diagnostic accuracy for cognitive impairment.[186] Another study concluded that self-reported cognitive symptoms do not predict objective performance.[191] Obermeit and colleagues (2017) determined that participants' self-reported cause of functional dependence with ADLs was not consistently related to objective cognitive performance; rather, it was related with mental health outcomes.[62] These findings suggest that while PLWH are able to recognize that they require functional assistance, they have difficulty determining the cause of their functional dependence.

Self-reported measures may have some clinical utility in identifying severe forms of cognitive impairment,[48] and other studies have found that they correlate with mood outcomes and neuropsychological performance among PLWH.[192,193] Of note, the Medical Outcomes Survey (MOS-HIV) cognitive subscale has been shown to correlate with overall neuropsychological performance in addition to abstraction, language, and visuospatial abilities among men with early HIV infection.[193] When compared with HIV-negative individuals, cognitive complaints among PLWH appear to be a more salient marker of actual cognitive deficits,[194] indicating that there is value in measuring both self-reported and objective cognitive performance in this population. Simioni et al. (2010) determined that self-reported cognitive complaints were predictive of objective cognitive impairment in 84% of their participants (72% of whom were male).[48] Previous work indicates that using multiple assessment methods including self-report and objective measures can maximize the sensitivity, quality, and utility of psychology measures.[195,196] Blackstone and colleagues (2012) evaluated self-reported and performance-based evaluations of function among PLWH with HAND and determined that the combined use of self-reported and performance-based measured classified more symptomatic PLWH with HAND, relative to either method alone.[197] Their study provides evidence for the use of combined methods to detect symptomatic cognitive impairment rather than self-reported methods alone. Finally, it is important to capture the patient's experience as an essential part of patient-centred care.[198] Self-reported cognition assessments may provide information to clinicians and researchers in addition to a standard neuropsychological assessment and may be used as a screening tool to identify those who require formal neuropsychological testing.

Chapter 3-Physical Deficits among People Living with HIV: A Review of the Literature and Implications for Rehabilitation

This chapter is a manuscript that was published in *Physical Therapy Reviews* in December 2019. The article outlines factors related to physical impairments and common physical deficits observed among PLWH. We also make recommendations regarding physical performance measures and exercise prescription.

Copyright Statement

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Contribution Statement

I developed and wrote the manuscript with assistance from Dr. Marilyn MacKay-Lyons.

Abstract

Background: Life expectancy has improved significantly among people living with HIV (PLWH). However, there is evidence of an accelerated aging process among PLWH, which includes physical impairments. Relative to the other consequences of aging among PLWH, physical impairments have not received much attention in the literature. There is an emerging need to study physical deficits in this population.
Objectives: The main purposes of this review are to explore factors contributing to physical dysfunction in this population, describe common physical impairments, discuss physical performance measures, and make recommendations for rehabilitation professionals regarding exercise prescription for PLWH.
Major Findings: Factors contributing to physical impairments include HIV severity, comorbidities, inflammation, and oxidative stress. Problems with muscle strength and mass, gait, static and dynamic balance, aerobic capacity, and frailty are common among PLWH and can have a negative impact on fall risk and functional performance. Several physical performance measures can be used for screening and assessment purposes, including the Short Physical Performance Battery, Six-Minute Walk Test, 5-times sit-to-stand, Community Mobility and Balance Scale, and gait speed tests.
Conclusions: Physical impairments are prevalent among PLWH. Rehabilitation providers should identify PLWH who are at risk of developing physical impairments. Exercise interventions including aerobic, resistance, and balance training appear to benefit PLWH. More research is warranted regarding the outcome measures that should be routinely used in clinical practice and the efficacy of exercise in this population.

Keywords: AIDS; balance; postural control; gait; frailty

Introduction

Since the advent of combination antiretroviral therapy (cART) in 1996, the life expectancy has improved significantly among people living with HIV (PLWH).[21] However, there is emerging evidence of an accelerated aging process, which includes physical impairments.[199] HIV is now categorized as a chronic condition, and PLWH are experiencing significant physical impairments (e.g., decreased muscle strength and mass, reduced aerobic capacity, and frailty) activity limitations (e.g., balance deficits, reduced walking speed) and participation restrictions (e.g., unemployment and social restrictions).[200]

HIV-associated physical impairments can have a significant impact on health-related quality of life, falls risk, and mortality. Balance deficits and mobility limitations are prevalent in the HIV population and are associated with increased fall risk, even in those with well-controlled viremia.[149] Slower walking speed and decreased grip strength are correlated with lower levels of physical health-related quality of life and increased mortality.[199,201,202] A large cohort study reported a dose-response relationship across all HIV disease strata between physical performance and mortality, and mortality risk was increased six-fold among PLWH with decreased physical performance compared to HIV-negative controls.[199]

Relative to the other consequences of aging among PLWH, physical impairments have not received much attention in the literature. The extended life span,[21] premature aging,[203] and increasing comorbidities[203] of PLWH, as well as the increasing incidence of HIV among older adults[117] support the need to gain a better understanding of the physical challenges facing this population. The main purposes of this review are to explore factors contributing to physical dysfunction in this population, describe common physical impairments, discuss physical performance measures, and make recommendations for rehabilitation professionals regarding exercise prescription for PLWH.

Search Strategy

Studies were identified by searching the following electronic databases: Embase, MEDLINE, and CINAHL. Reference lists were also hand-searched for additional studies. Searches included terms such as “physical function”, “sarcopenia”, “muscle weakness”, “aerobic function”, “falls”, “frailty”, “balance”, “gait”, and “HIV” and other related terms. The last search was conducted in March, 2019.

Factors Contributing to Physical Dysfunction

HIV Severity

HIV severity is determined by immune function (cluster of differentiation-4, CD4+ count]) and viral load (HIV copies/ml of blood).[204,205] There is evidence of a direct relationship between HIV severity and physical function, with HIV infection itself being independently associated with a 30% increase in odds ratio of decreased physical performance.[199] One systematic review and meta-analysis[206] reported that 53% of included studies found a positive relationship between HIV severity and physical performance outcomes among PLWH.[149,207–212] Fortunately, improved immune function and virological suppression benefits physical performance – one cross-sectional study of 513 PLWH found that higher CD4+ counts and undetectable viral loads (<50 HIV copies/ml of blood[23]) were associated with better self-reported physical function.[148] Therefore, appropriate pharmacological management is important in the prevention of physical deficits among PLWH.

Chronic Inflammation and Oxidative Stress

Preliminary evidence suggests that inflammation is associated with decreased functional performance among PLWH. In older adults, elevated inflammatory markers have been linked to frailty and functional decline.[213,214] Inflammation has been observed among PLWH, even among those with adequate immune function and virological suppression.[215] Researchers have found an association between increased inflammatory markers (interleuken-6 and tumour necrosis factor receptor-1 and -2) and decreased physical function and muscle mass in middle-aged PLWH[216,217] – evidence of "inflamm-aging".[218]

HIV and aging are each associated with increased oxidative stress and mitochondrial damage.[219–221] Viral gene products can damage mitochondria, thereby promoting oxidative stress.[220] Further, some cART medications themselves may be mito-toxic, which can increase oxidative stress and promote a chronic inflammatory state.[222] Of note, a meta-analysis did not find an association between cART use and improved balance and gait performance among PLWH, suggesting that cART may be more potent in preventing physical deficits than reversing pre-existent physical dysfunction.[206]

Peripheral and Central Nervous System Factors

HIV-associated sensory neuropathy is characterized by neuropathic pain, numbness, and sensory loss in the distal extremities.[223] HIV infection and certain cART medications are thought to contribute to peripheral neuropathy.[224] Although peripheral neuropathy is thought to affect balance and walking performance among PLWH, a meta-analysis by Berner and colleagues noted that none of the five cross-sectional studies on this topic reported such an association.[206] In comparison, Tassiopoulos and colleagues observed in their prospective study (which is a higher level of evidence than cross-sectional work) that frail PLWH with peripheral neuropathy were at greater risk of falling than non-frail individuals, whereas this association was not observed in PLWH without peripheral neuropathy.[225] It may be that physical performance dysfunction is precipitated by the presence of both frailty and peripheral neuropathy, rather than peripheral neuropathy alone.

The lack of association between peripheral neuropathy and balance performance among non-frail PLWH intimates central nervous system involvement in balance impairments.[207,226–229] Further evidence is that PLWH often demonstrate balance impairments during eyes closed conditions.[207,210,226,229,230] As well, Sullivan and colleagues observed that the average tissue ratio of the cerebellum and pons in 123 PLWH was 3% less than that of HIV-negative controls and was significantly predictive of balance and fine motor skills.[207] A systematic review by Heinze et al. indicated that PLWH of all ages and HIV stages experience vestibular dysfunction that contribute to vertigo, dizziness, and postural imbalance.[231] Almost 50% of PLWH were found to exhibit peripheral vestibular dysfunction (disorders of the semicircular canals or otolithic organs[232]), with reported prevalence of central nervous system vestibular dysfunction being even higher.[231]

Comorbidities

PLWH have a higher prevalence of comorbidities than their HIV-negative counterparts.[233,234] The most common comorbidities and their respective prevalence among middle and older-aged PLWH include hypercholesterolemia (42-66%), depression (38-46%),[235] hypertension (45%), obstructive pulmonary disease (34%), and osteoporosis or non-traumatic fracture (18%).[233] A study of 262 younger and older PLWH and HIV-negative age-matched participants determined that approximately 50% of older PLWH had at least one comorbidity, compared to 22% in older HIV-negative individuals, 18% in younger PLWH, and 13% in younger HIV-negative individuals.[234]

Cardiovascular disease has been shown to predict lower physical function in both PLWH and HIV-negative individuals, whereas chronic pulmonary disease has a particularly detrimental effect on function among PLWH.[236] Renal disease and hepatitis C are related to poorer self-reported physical function among PLWH, but not HIV-negative individuals.[237] Obesity is also a well-known predictor of decreased physical function among PLWH.[208,237,238] Other contributors to poor physical function include older age, diabetes diagnosis, and neurological opportunistic infections indicative of acquired immune deficiency syndrome (AIDS),[149] as defined by the Centers for Disease Control[19].

Physical Dysfunction among People Living with HIV

Figure 1 outlines potential mechanisms and physical deficits observed among PLWH. Below the main deficits are summarized. The classification of stages of HIV infection is also specified, when appropriate: *asymptomatic* (no symptoms or acute HIV symptoms), *symptomatic* (presence of an HIV-related condition), and *AIDS* (CD4+ count $<200/mm^3$ or an AIDS-defining illness).[19,239,240]

Rehabilitation providers should identify PLWH at risk of developing physical impairments, including those with severe HIV (low CD4+ count, high viral load),[204,205] older age, and comorbidities for additional physical screening. There are cues from the literature suggesting which physical performance measures should be used for screening and assessment. Refer to table 1 for useful physical performance measures, their scoring and normative values, and responsiveness based on research conducted with HIV-negative individuals.

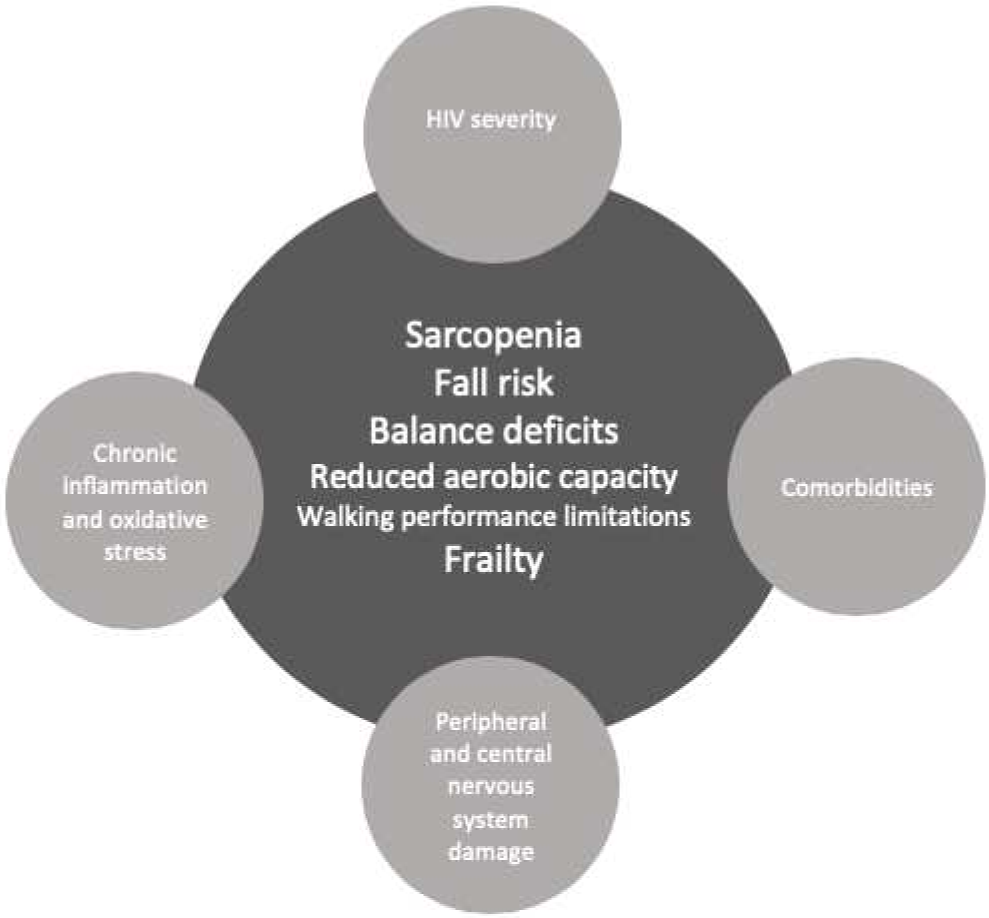

Figure 1: Overview of mechanisms and physical deficits among People Living with HIV

Sarcopenia

Sarcopenia is defined as the presence of both reduced muscle mass and muscle function.[241] Among PLWH, muscle strength and mass are reduced with age and are related to physical impairments, although the prevalence of sarcopenia varies depending on the diagnostic methods and criteria.[242] A randomized controlled trial (RCT) of older sedentary PLWH and age-matched HIV-negative controls (93% male) revealed that PLWH had reduced baseline muscle strength on bench press, leg press, and lateral pulldown tests versus controls.[243] A body composition study determined that 20% of 66 middle-aged male PLWH had reduced muscle mass.[244] Erlandson et al. revealed in their nested analysis of 30 low-functioning and 48 high-functioning PLWH (85% male) that 35% of the total participants had low muscle mass, and 50% of the low-functioning participants met the diagnostic criteria for sarcopenia.[245] A longitudinal study of changes in muscle mass (but not strength) also reported lower mass in PLWH (64% male) versus HIV-negative controls at baseline but no between-group difference in rate of muscle mass loss after five years.[246] In the same study, certain cART medications and a higher CD4+ count were associated with increased muscle mass,[246] which may indicate that muscle mass is better preserved among PLWH on cART.

Some gender differences in sarcopenia rates may exist among PLWH. A dual-energy X-ray absorptiometry study involving 860 PLWH determined that sarcopenia was significantly more prevalent in female than male PLWH over 50 (43% versus 8.8%).[242] This indicates that female PLWH may be at a higher risk of developing sarcopenia than males.

Changes to muscle contractile properties and gene expression may contribute to reduced muscle strength and function among PLWH. In comparison to HIV-negative controls, PLWH are more likely to have intramuscular contractile impairments involving muscle force relaxation[247] and premature upregulation of genes associated with muscular aging,[248] which can lead to muscular fibrosis.[249] As well, fat infiltration into the muscle and cART-related mitochondrial dysfunction may contribute to myopathy among PLWH.[250]

Decreased muscle strength influences functional performance among PLWH. A large prospective cohort study found that weak grip strength was associated with higher odds of recurrent falls among middle-age PLWH.[225] Further, Richert and colleagues (2014) attributed their observations of a significant decline in mobility of PLWH over a two-year period to decreased lower extremity muscle strength.[227] Given the extent of muscle impairments in the HIV population, clinical muscle strength and mass assessments should be performed. Also, further investigation is warranted of the potentially mediating roles of muscle strength and lean mass on balance and walking performance among PLWH.

Increased Fall Risk

PLWH are susceptible to falls and fragility fractures[225,251] due to sarcopenia and central nervous system changes, underlining the importance of considering balance control in this population. A cross-sectional study of 359 middle-aged PLWH (85% male) revealed that 30% of participants reported falling once or more in the previous twelve months, and 18% were recurrent fallers.[251] The fall rates among PLWH aged 45-65 years on cART in that study were similar to HIV-negative adults ten years older.[251] Another cross-sectional study revealed that 41% of 359 PLWH aged >50 years reported a fall in the past year.[252] Moreover, PLWH are at a higher risk of sustaining an injury following a fall, due to high rates of osteoporosis (three times that of the general population), decreased muscle strength, peripheral neuropathy, cognitive impairment, and frailty.[225,244,251,253,254] Fracture incidence is higher among both male and female PLWH than HIV-negative controls.[255,256] Due to the high risk of falls and fractures, strategies for falls prevention among PLWH should be a priority.

Both the *5-times sit-to-stand* (*5STS,* time to complete five sit-to-stand-to-sit cycles at a fast speed)[257] and *the six-minute walk test* (*6MWT,* distance walked in six minutes)[258] may be helpful in identifying fall risk among PLWH. The 5STS is a time-efficient physical performance measure and significant predictor of fall risk in community-dwelling older adults.[259,260] It has also been recommended for use with PLWH.[149,199,227,261,262] Richert and colleagues (2011)[227] determined in their cross-sectional study that 53.3% of participants exceeded a cut-off of two standard deviations above the HIV-negative mean on the 5STS - the only outcome measure in which more than half of the participants demonstrated poor performance.[263] A 2-year longitudinal study by the same team[149] revealed that 31% of 178 participants (80% male) experienced a deterioration in 5STS of more than 2 seconds, approximating the minimal detectable change of 2.5 or more seconds reported for elderly females.[264] Comparatively, Bauer and colleagues did not find differences between PLWH and HIV-negative individuals in terms of the 5STS,[208] and Tanon et al. found that only 9.7% of PLWH demonstrated impairments on the 5STS.[265] Richert et al. (2014) determined that 6MWT distances were significantly worse in those who reported falling during the previous twelve months, compared to non-fallers.[149] As well, a cross-sectional analysis of 107 cART-treated PLWH (70% male) by Khoury et al. noted that PLWH performed worse than normative values on the 6MWT.[266]

Screening for falls and osteoporosis is critical in the HIV population, especially for symptomatic and older PLWH. We recommend that clinicians ask PLWH about fall history over the past twelve months,[267] as twelve-month fall recall among healthy elderly individuals is more accurate than 3- and 6-month timelines.[268] The primary care guidelines for PLWH also recommend screening all individuals over 50 for osteoporosis.[269] We recommend collaboration with physicians for screening and prevention of falls and osteoporosis.

Static Balance Deficits

Balance is often divided in two classes - static balance is the maintenance of the center of mass within the base of support during quiet standing and dynamic balance is the maintenance of postural stability with the center of mass over the base of support during movement.[270] Assessments of static and dynamic balance have proven useful in predicting activities of daily living (ADL) performance and premature mortality among HIV-negative individuals.[271–274] Although no validation studies of these tests have been conducted in the HIV population, several investigators have used clinical balance measures to explore postural control and monitor change over time among PLWH. The following is a summary of findings of these studies.

Three studies using *force plates* to document static balance deficits in individuals across stages of HIV concluded that PLWH demonstrate increased excursion and postural sway velocity.[228–230] Berner et al.[206] performed a meta-analysis of two of those studies [229,230] and concluded that medically asymptomatic PLWH performed similar to controls whereas symptomatic individuals demonstrated greater sway with or without visual occlusion compared to controls and asymptomatic PLWH.[229,230] Another cohort study of 86 PLWH (54% male) determined that sway strategy scores were significantly lower among PLWH compared to HIV-negative controls during 4 and 5 subtests of the *Sensory Organization Test* (i.e., eyes closed on unsteady surface and altered vision on unsteady surface, respectively).[275] The findings of these postural sway studies intimate that PLWH, particularly those who are symptomatic, are less capable of adapting to challenging conditions,[276] relying more on hip than ankle balance strategies to maintain postural control.

Using the *Single Leg Stance (SLS)* test,[277] Bauer et al.[208] noted a significant decrease in stance time on the non-preferred leg among PLWH with obesity in cohorts of 86 PLWH and 121 HIV-negative individuals (54% male).[208] Similarly, Tanon et al. reported that 87% of 308 PLWH (68% female) had impaired SLS tests with eyes closed compared to HIV-negative normative values.[265] Cohen et al.[210] observed a higher frequency of impaired performance during the *Romberg Foam Test* [278] in 247 PLWH (51% male) compared to 200 HIV-negative controls (84% male). Although Sullivan and colleagues[207] reported significantly lower SLS times among 40 female and male PLWH (70% male) compared to HIV-negative individuals, significant group differences were not demonstrated on the *Tandem Stance Test.*[279] In general, static balance among PLWH deteriorates with increased task demands such as a visual occlusion or standing on foam surface.[210]

Dynamic Balance Deficits

It is not currently known if sex and gender differences exist in static or dynamic balance among PLWH. Tanon et al. did not reveal differences between male and female participants on the 5STS, TUG, or SLS with eyes closed.[265] More research is needed to determine if sex and gender influence balance performance in this population.

Although the *Berg Balance Scale (BBS)* is one of the most commonly administered dynamic balance tests,[280] only two studies were cited that used the BBS in the HIV population.[227,281] In their cross-sectional study of 324 PLWH, Richert and colleagues (2011) determined that only 1.5% of PLWH scored less than 46 and the median score of the sample was 56 (the maximum attainable score).[227] The previously mentioned systematic review by Berner et al. concluded that BBS scores among most PLWH do not deviate from established norms for HIV-negative individuals and that ceiling effects may have biased their findings.[206] This evidence suggests that the BBS is not the optimal measure of balance for PLWH.

Another dynamic balance and mobility measure, the *Timed up and Go (TUG)*,[282] involves standing from a chair, walking 3 meters, turning around and walking back to sit down.[283] In their cross-sectional study, Richert and colleagues (2011) reported that only 10.5% of PLWH demonstrated poor performance on the TUG, with a median time of 5.6 seconds,[227] whereas Tanon et al.[265] revealed that 29% of their sample of cART-treated participants demonstrated poor performance on the TUG compared to unreferenced normative values (median = 13.3 seconds). These discrepant results may be attributed to different demographic characteristics in the studies by Tanon et al. and Richert et al. - 68% female, median age 45, and median body mass index of 24 versus 20% female, median age 48, and median body mass index of 22.5, respectively. The *Functional Reach Test,*[284] which measures the maximal forward reach, does not reveal impairments in PLWH.[285] In contrast, the *Limits of Stability test,*[208] which involves measuring a participant's maximum excursion,[286] has been shown to challenge dynamic balance among PLWH, as has the *Heel-To-Toe Walk Test* with eyes closed (tandem walking),[207] and the *360-Degree-Turn Test.*[208]

The *Short Physical Performance Battery (SPPB*) has been used in studies with PLWH[199,261,262] and includes double leg stance, semi-tandem and tandem balance tests, 4-

meter gait speed, and the 5STS. Brañas and colleagues determined that more than half of older PLWH scored a 9 or fewer points out of 12 on the SPPB.[262] Ceiling effects can be avoided by adapting existing cut-off scores on the SPPB to PLWH, as Greene and colleagues did by adding a SLS balance test, increasing balance times, and increasing the number of stands in the 5STS.[199] They also established a cut-off of 10/12 points on the SPPB for physical deficits among PLWH.[199] Among older adults, a change of 1 point on the SPPB is clinically relevant,[287] and can be applied to PLWH.

The *Community Balance and Mobility scale* (CB&M)[288], a high-level balance assessment, has been used with older HIV-negative individuals and is less susceptible to ceiling effects than the BBS.[289,290] The only known study that used the CB&M with PLWH (n = 22, 68% male) determined that baseline values were lower than normative values for healthy adults in all but one age category.[291] There is currently no gold standard balance performance assessment for PLWH but the CB&M is a promising tool for measuring high-level mobility and balance in this population. Its utility in measuring postural control among PLWH should be evaluated further.

Reduced Aerobic Capacity

PLWH of all ages have reduced aerobic capacity compared to age-matched controls,[240,292,293] with larger impairments demonstrated by older PLWH.[294] A meta-analysis of 21 studies revealed that peak oxygen uptake (VO_2peak) levels in PLWH (mean, 26.4 ml/kg/min,) are among the lowest in clinical populations.[295] Given that the threshold VO_2peak for independent living is about 20 ml/kg/min,[296] a mean VO_2peak of 26.4 ml/kg/min implies a compromise in VO_2 reserve, which can have significant implications for ADL and functional independence. Studies of adolescent PLWH documented VO_2peak values 24-44% below age-predicted norms[297] and a decreased ventilatory threshold during light instrumental ADLs such as house cleaning and employment.[298] Reductions in ventilatory threshold and VO_2peak among PLWH result in exercise intolerance, which can significantly impact rehabilitation and participation in recreational activities.[240] A decreased ventilatory threshold results in premature activation of anaerobic systems to supplement aerobic energy systems, which in turn leads to earlier onset of fatigue during ADLs.[240]

Cade and colleagues (15 females, 24 males) observed that VO_2change during submaximal exercise was significantly lower among both cART-treated and untreated PLWH compared to controls, prompting the authors to conclude that HIV, not cART, contributed to the impaired oxygen kinetics.[299] However, this conclusion is contradictory to another conclusion by the same group that cART contributed to reduced oxygen extraction in their sample of 18 female and 27 male PLWH.[300] Reasons for this discrepancy are unknown but considering the small sample sizes, more research is needed to evaluate the impact of HIV and cART on oxygen kinetics in this population.

Decreased aerobic function is accompanied by a reduction in stroke volume, decreased oxygen kinetics,[299] lower arterio-venous oxygen extraction, and reduced muscle oxygen utilization.[300] Some studies have linked these aerobic changes to cART, which can adversely affect skeletal and cardiac muscle mitochondria.[240,301] Other studies have determined that these aerobic changes are due to cART-induced lipodystrophy (metabolic and body composition changes[302]) and atherosclerosis.[303] Reduced muscle strength may also reduce lower extremity blood flow, thereby reducing the lactate threshold, and reducing an individual's ability to reach their VO_2peak.[299,304]

Walking Performance Limitations

In the general population, gait performance deteriorates with age, and a steeper deterioration in fast gait speed is associated with disability, as observed in a sample of 3,814 community-dwelling older adults.[305] Studies using standardized measures of physical performance indicate worse gait dysfunction among PLWH than HIV-negative individuals. Brañas et al. determined in their study of 117 older PLWH that 20.5% demonstrated reduced gait speeds (using a cut-off of 0.8 meters per second) compared to established norms in older adults.[262] The meta-analysis by Berner et al.[206] determined that three[209,212,251] of eight studies[149,201,208,209,212,226,251,261] indicated reduced maximal gait speeds among PLWH versus controls. Interestingly, one cross-sectional study reported that only PLWH with obesity demonstrated impairments in fast cadence and fast gait initiation time compared to HIV-negative controls.[208] Berner et al. concluded that despite the success of cART, PLWH demonstrate impairments in fast gait speed, but not comfortable gait speed.[206] Gait deficits could have significant real-world consequences, as decreased walking speed is associated with a higher falls risk among PLWH.[225,227]

In a previously mentioned study, Richert et al. (2011) revealed poor performance on the 6MWT in 23.6% of PLWH.[227] A subsequent meta-analysis of two studies evaluating 6MWT[212,306] revealed significantly reduced distances among PLWH versus controls.[206] Although regarded as a measure of physical endurance, the 6MWT is associated with gait speed in other clinical populations.[307,308] Richert and colleagues (2014)[149] also recorded a deterioration in the 6MWT distance of 11 meters per year during their 2-year prospective study of middle-age PLWH – over double the expected decline of 5 meters per year in the general population.[309]

To date, gait speed tests and the 6MWT have not been validated in PLWH, but they may have some clinical utility in this population. Fast gait speed should be used rather than a comfortable pace, especially among high-functioning or middle-aged PLWH.[267] Khoury and colleagues suggest that for meaningful improvement in physical performance among PLWH, a change of at least 0.1 meters per second in gait speed and 50 meters in 6MWT distance be used.[266,287,310] Further research is needed to investigate the nature of these physical deficits and to validate assessment tools specifically for PLWH.

Frailty

Frailty, defined as a syndrome of reduced physiological reserve, is an emerging concern, especially among older PLWH.[311] Fried et al. characterize frailty as a composite clinical phenotype involving unintentional weight loss (≥4.5 kg or ≥5% of body weight during the previous year), muscle weakness (reduced grip strength), decreased endurance and exhaustion, slow gait speed, and low physical activity.[312] According to the Fried classification, three of these five criteria are required for the designation of 'frail', and one or two criteria for the designation of 'pre-frail'.[312]

There is a relationship between HIV infection and the early progression to frailty.[313] A prospective multi-centre cohort study reported that 6% of 967 PLWH >40 years were frail, and 39% were pre-frail according to the Fried criteria.[225] Importantly, the prevalence of frailty among PLWH in that study is similar to the frailty rates seen in HIV-negative individuals ten years older.[314] Frailty rates also increase with age; a cross-sectional study of 117 ambulatory PLWH aged >55 demonstrated that 15.4% met the Fried frailty criteria and 52.1% were pre-fail[262] and another study determined that up to

60% of PLWH over fifty were frail.[315] The consequences of frailty are significant; frail and pre-frail PLWH are more likely to have recurrent falls compared to non-frail individuals.[225]

Screening for frailty should also be a priority for rehabilitation professionals working with PLWH. Rees et al. recommend identifying patients at high frailty risk, including those with a CD4+ count below 200, unintentional weight loss, severe peripheral neuropathy, and cART non-adherence.[316] Regarding gait evaluation for frailty among PLWH, the 6MWT and gait speed tests such as the 10-meter and 4-meter walk tests have some clinical utility. These tests are commonly used in the literature and provide a useful comparison across samples. When asking about physical activity, it is important to ask about current participation in aerobic, resistive, and balance exercise. We recommend screening and measuring physical impairments and activity levels in order to prescribe appropriate exercise interventions.

Table 1: Outcome measures with age and gender-based norms for HIV-negative individuals

Physical Performance Test	Scoring	Age-based norms	Age-Based Norms for Men	Age-Based Norms for Women	Responsiveness
Fast gait speed [287,317]	**Metres/second**	**N/A**	**20-29: 2.53 30-39: 2.46 40-49: 2.46 50-59: 2.07 60-69: 1.93 70-79: 2.08**	**20-29: 2.47 30-39: 2.34 40-49: 2.12 50-59: 2.01 60-69: 1.77 70-79: 1.75**	**Small meaningful change: 0.05 m/s Substantial meaningful change: 0.10 m/s**
Six-Minute Walk Test[287,318]	**Distance walked (metres)**	**N/A**	**60-69: 572 70-79: 527 80-89: 417**	**60-69: 538 70-79: 471 80-89: 392**	**Small meaningful change: 20m Substantial meaningful change: 50m**
Short Physical Performance Battery[287,319]	**Score out of 12**	**N/A**	**<68 years: 10.4 >68 years: 8.4**	**<68 years: 9.7 >68 years: 7.5**	**Small meaningful change: 0.5 Substantial meaningful change: 1**
Grip Strength[320,321]	**Kilograms**	**N/A**	**18-24: 47.0 25-29: 49.7 30-34: 46.5 35-39: 47.1 40-44: 46.7 45-49: 42.8 50-54: 44.0 55-59: 40.7 60-64: 38.4 65-69: 36.8 70-74: 34.7 75-79: 32.7 80-85: 28.1**	**18-24: 28.1 25-29: 29.6 30-34: 28.9 35-39: 29.2 40-44: 29.9 45-49: 28.8 50-54: 28.2 55-59: 25.1 60-64: 23.6 65-69: 22.1 70-74: 21.5 75-79: 19.6 80-85: 19.9**	**Clinically meaningful change: > 6 kilograms**
5-Times Sit-to Stand[263,264]	**Seconds**	**19-49: 6.2 50-59: 7.1 60-69: 8.1 70-79: 10.0 80-89: 10.6**	**N/A**	**N/A**	**Minimal detectable change: 2.5 seconds**
Community Balance and Mobility Scale[290,322]	**Score out of 96**	**20-29: 88.7 30-39: 86.3 40-49: 84.4 50-59: 77.4 60-69: 64.9 70-79: 49.8**	**N/A**	**N/A**	**Score ≤ 39 identifies individuals with impaired gait, balance, and mobility**

N/A, not applicable

Major Findings

In summary, several factors contribute to the clinical presentation of physical deficits of PLWH. Among these factors are HIV severity, chronic inflammation and oxidative stress, peripheral and central nervous system dysfunction, and the presence of comorbidities. Common physical deficits that can manifest in PLWH of all ages despite cART treatment include sarcopenia, fall risk, static and dynamic balance deficits, reduced aerobic capacity, walking performance limitations, and frailty. These deficits occur prematurely and accumulate during the aging process, heightening fall risk, reducing functional mobility, and increasing mortality. Muscle strength and mass impairments are common and can affect functional performance among PLWH. Static and dynamic balance impairments are particularly apparent under challenging conditions such as unstable surfaces and visual occlusion. Gait impairments are especially evident at fast speeds, especially among PLWH with obesity. Many PLWH have reduced aerobic capacity, which can reduce their ability to perform ADLs. PLWH, particularly those who are untreated with cART, are also at risk of frailty. Several physical performance measures can be used for screening and assessment purposes, including the SPPB, 6MWT, 5STS, CB&M, and gait speed tests.

Considerations for Rehabilitation Providers

Considerations for rehabilitation providers regarding exercise prescription for PLWH will be outlined in this section.

Exercise Recommendations

There is burgeoning evidence from the interventional literature that supports the use of aerobic and progressive resistive exercise (PRE) for improved physical function among PLWH. A recent meta-analysis by O'brien and colleagues provides a comprehensive summary of the evidence from 20 RCTs regarding progressive resistance exercise for PLWH.[323] The authors concluded that PRE three days per week for four weeks in total resulted in significant improvements in upper and lower extremity strength and body composition among PLWH.[323]

A 12-month RCT involving a home-based walking program revealed improvements in physical activity, 6MWT distance, waist-to-hip ratio, and cardiovascular risk factors among 84 older PLWH (79% female).[324] An innovative RCT enrolled sedentary, older, and mostly male PLWH and healthy controls who engaged in a 12-week program of moderate-intensity aerobic and resistance exercise after which they were randomized to continue moderate-intensity exercise or progress to a higher intensity for another 12 weeks.[243] PLWH had larger improvements in aerobic capacity versus controls during the first 12 weeks and greater increases in stair climb and 400-meter walk time during the second 12 weeks, and PLWH randomized to the high-intensity program had significantly larger improvements in strength than the PLWH in the moderate-intensity group, while controls saw no difference in strength gains with increased intensity.[243] This evidence indicates that PLWH may benefit more from high-intensity interventions than healthy individuals.

Exercise prescription should be based on the stages of HIV infection (asymptomatic, symptomatic, and AIDS). Based on the available research, we endorse 2015 guidelines for exercise therapy for people with HIV/AIDS.[325] These guidelines recommend that *asymptomatic PLWH* engage in aerobic exercise 5 days per week at 65-80% of heart rate reserve (HRR), and PRE 3 days per week at 65-85% of 1-repetition maximum (1-RM) for a total combined (aerobic and resistance) session of 30-90 minutes.[325] *Symptomatic PLWH* should participate in aerobic exercise 3-5 days per week at 55-70% of HRR and PRE at 55-85% of 1-RM for a total combined session of 30-90 minutes.[325] A lower dose is recommended for *individuals with AIDS* -3 days per week at 30-45% of HRR and 2 days per week of PRE at 35-50% of 1-RM for a total combined session of 20-30 minutes.[325] For deconditioned PLWH, rehabilitation providers should consider adapting their training programs to a lower ventilatory threshold.[240] Training should last at least 6 weeks for benefits to aerobic and muscle strength.[326]

While the effect of aerobic and PRE has been well studied, there has been a dearth of studies evaluating the effect of balance training on balance performance among PLWH. Veeravelli et al. conducted a single-group pre-post study with 10 PLWH who performed game-based balance and gait training twice weekly for six weeks and observed decreased center of mass sway with eyes closed during the semi-tandem test and enhanced gait speed.[327] A case study determined that four weeks of yoga resulted in improved Multidirectional Reach Test performance among two of three PLWH with neuropathy.[328] Despite the study design and small sample size, these studies provide preliminary evidence that balance training twice weekly can improve dynamic balance and walking performance among PLWH.

Research on balance training conducted in other populations and can inform exercise prescription for PLWH. Balance training three times weekly for 30-45 minutes for a total of 91-120 minutes per week for 11-12 weeks is effective in augmenting balance performance among older adults.[329] Furthermore, a meta-analysis revealed that exercise decreased fall rates among older adults by 21%.[330] Based on this limited literature we recommend that PLWH perform balance exercises for at least 30 minutes, 3 times weekly for at least 11 weeks.

Conclusion

PLWH are grappling with physical impairments at an earlier age than their HIV-negative counterparts. Limitations in muscle strength, balance, aerobic capacity, and walking performance coupled with frailty are common and can impact fall risk and functional performance. Contributors to these physical impairments are understudied, but are thought to include HIV severity, inflammation, oxidative stress and comorbidities.

Aerobic, resistive, and balance exercise training can help stave off these physical impairments among older adults with levels of physical deficits similar to PLWH. More research is warranted regarding the outcome measures that should be routinely used in clinical practice and the efficacy of exercise in this population.

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Conflict of Interest

The authors have no conflict of interest.

Chapter 4-Medication Adherence, Physical Activity, Health-Related Quality of Life, and Mental Health among People Living with HIV

Many PLWH have challenges related to medication adherence, physical activity, health-related quality of life (HRQOL), and mental health. This chapter will outline the effect of chronic HIV infection on these outcomes, as well as contributing risk factors, and commonly used outcome measures used in the literature.

cART Adherence

A systematic review conducted by Mills et al. (2006) determined that only 55% of North American and 77% of sub-Saharan African PLWH were achieving minimum cART adherence levels (using a cut-off of ≥ 80% adherence).[331] A meta-analysis of 43 studies published in 2016 concluded that optimal (≥ 80%) cART adherence worldwide was only attained by 63% of PLWH.[332] According to a meta-analysis of 53 studies conducted with PLWH in Latin America and the Caribbean, overall cART adherence was 70%.[333] Similarly, a cross-sectional study of 116 PLWH in India conducted by Achappa and colleagues (2013) determined that only 64% of participants reported achieved their benchmark of 95% cART adherence.[334] It is clear that PLWH are not achieving optimal cART adherence levels.

Many studies have evaluated risk factors for cART non-adherence. In the cross-sectional study by Achappa and colleagues (2013), (31% of participants were female) among participants with low adherence, 33% of individuals forgot to take their pills, and 30% identified financial constraints as a barrier.[334] Other reasons identified for sub-optimal adherence included a lack of family support, social stigma, depression, alcohol use, and cART side-effects.[334] A systematic review of 146 studies conducted with PLWH living in sub-Saharan Africa determined that the strongest predictors of non-adherence included alcohol use, male gender, traditional or herbal medicine use, lack of satisfaction with health care facilities and providers, depression, stigma, and lack of social support.[335] cART-related adverse events such as gastrointestinal symptoms and lipodystrophy have known effects on medication adherence as well.[336] Interestingly, older age appears to reduce the risk of cART non-adherence by 27%, according to a meta-analysis of 12 studies.[337]

Adherence to cART medication is strongly associated with HIV treatment outcomes and mortality. Poor cART adherence has been associated with suboptimal viral suppression,[338] AIDS progression,[339] and survival.[340] Importantly, cART non-adherence elevates the risk of viral resistance and the transmission of drug-resistant strains of the virus.[341–343] Fortunately, emerging research is indicating that cART adherence and viral suppression have significantly improved over time. Some of these improvements may be attributed to the combination of medications into a single pill; enhanced adherence has been observed among PLWH on once-daily cART regimens, according to a meta-analysis of 19 RCTs.[344] However, significant disparities remain for vulnerable groups, including sex workers, individuals who inject drugs, and men who have sex with men.[345]

Medication Adherence Outcome Measures

Objective methods of measuring cART adherence levels include biological assays, or blood and urine markers.[346] Other objective measures include electronic drug monitoring, where a computer microchip is embedded in the cap of a pill bottle or other container, then the date and time are recorded. Electronic drug monitoring is considered the gold standard and is often used as a comparison with self-reported medication adherence measures.[347,348] The focus of this section will be on self-reported measures of cART adherence.

The Simplified Medication Adherence Questionnaire (SMAQ) is a simple six-item self-reported questionnaire that was validated with PLWH.[349] An individual is deemed non-adherent if they indicate a positive response to any of the questions, have missed one or more doses over the past week, or have missed all of their medications on more than two days during the past three months.[349] The SMAQ has acceptable internal consistency (cronbach's alpha=.75) and inter-rater reliability [88.2% (kappa=.74)] as determined by a sample of over 3000 PLWH (72% of whom were male).[349] The questionnaire also has 91% specificity, 72% sensitivity, and a likelihood ratio of 7.94 to identify non-adherent individuals, when compared with an electronic medication monitoring system.[349] Furthermore, the SMAQ is inexpensive, takes less than five minutes to administer, and is a stronger predictor of virological failure (defined as a viral load more than 500 copies/ml in this study) in one year than age, sex, baseline CD4+, and baseline viral load.[349] The questionnaire has been used extensively with the HIV population.[349–352]

The visual analogue scale (VAS) has also been used to measure cART adherence among PLWH, whereby participants are asked to indicate their adherence percentage over the previous four weeks on a linear scale.[353] VAS scores are positively associated with both objective medication monitoring systems and pill counts, and are inversely associated with viral load.[353] Furthermore, a meta-analysis of 20 studies revealed large effect sizes regarding the relationship between VAS scores and other self-reported measures and objective monitoring methods of cART adherence.[354] The Adult AIDS Clinical Trial Group (AACTG) questionnaire asks participants to report missed doses in the past four days.[355] A prospective observational cohort study of 184 newly-diagnosed predominantly Hispanic, 80% male PLWH determined that both VAS and AACTG measures were strongly associated with medication monitoring systems and pharmacy data.[347]

Self-reported medication adherence questionnaires can have many advantages, including low cost, ease, and fast administration.[356] There is evidence that self-reported adherence relates to virological suppression; a study found a strong relationship between self-reported cART non-adherence and detectable viral load in a sample of 60% male PLWH living in China.[357] Challenges related to self-reported cART adherence measures include their propensity to biases such as social desirability and recall error, which threaten their internal validity.[358] In fact, some studies have determined that self-reported estimates of adherence are 10-20% higher than electronic drug monitoring methods.[356,359] As a result, self-reported cART adherence measures have good specificity and negative predictive value but poor sensitivity and positive predictive value for poor adherence.[346,357]

Physical Activity

The World Health Organization guidelines recommend that adults perform 150 minutes of moderate-intensity aerobic physical activity per week or 75 minutes of vigorous-intensity aerobic per week.[360] Fewer PLWH are meeting the World Health Organization physical activity recommendations than HIV-negative individuals (51% vs. 65%).[361] In addition, PLWH spend only 98.9 minutes per day on average being physically active as measured by accelerometers, which is lower than most chronic disease populations, according to a meta-analysis of 24 studies by Vamcampfort et al. (2018).[362] Of note, in the same study, their meta-regression revealed that steps per day were not moderated by gender.[362] Another meta-analysis conducted by Vamcampfort and colleagues (2017) of 6 cross-sectional studies determined that PLWH spend 533 minutes per day on average being sedentary, using self-reported and objective methods of data collection.[363] Physical activity levels are even lower among older PLWH; a study of 21 older PLWH (67% of whom were male) determined that only 14% of participants achieved 150 minutes of moderate intensity physical activity per week, and on average took only 3,442 steps per day.[364] PLWH also have significantly lower physical activity levels compared to HIV-negative individuals when measured using self-reported questionnaires, such as the Rapid Assessment of Physical Activity (RAPA).[361] Furthermore, PLWH are also less likely than HIV-negative controls to perform resistance training or flexibility exercises (49% vs. 66%, respectively) using the RAPA.[361]

Physical inactivity can affect cART non-adherence, quality of life, and HIV progression. A large cohort study of 860 PLWH determined that low self-reported physical activity levels predicted depression and cART non-adherence, and subsequently, higher viral loads.[365] A study conducted with 110 PLWH and 110 HIV-negative controls (of whom, 96% were male) determined that visual analog scores for quality of life were significantly lower among PLWH who did not meet the World Health Organization physical activity guidelines compared to PLWH who met the guidelines, while this relationship was not seen among HIV-negative individuals.[361] Negative factors associated with physical inactivity among 1,133 PLWH (69% male) living in Vietnam (measured using the IPAQ or the International Physical Activity Questionnaire) included urban living, having HIV symptoms, poor cART adherence, and longer cART duration.[366] A recent focus group study determined that HIV symptoms, cART side effects, and fatigue were significant barriers to physical activity, while facilitators included family support and self-monitoring techniques.[367]

Physical Activity Outcome Measures

The IPAQ was developed to estimate vigorous activity, moderate activity, and walking activity among HIV-negative individuals aged 15–69 years old.[368] A study evaluated construct and concurrent validity of the IPAQ among 46 healthy HIV-negative individuals and determined a strong association between activity monitor data and IPAQ scores for total physical activity and vigorous physical activity while a weaker association was observed for moderate physical activity.[369] The IPAQ may under- and over-report physical activity levels among older adults, as evidenced by a study that used interviews to document physical activity reports.[370] It has been used in previous literature with PLWH;[151,153] but a study conducted by Fillipas and colleagues determined that it also overestimates moderate and vigorous physical activity levels compared to accelerometry data among PLWH (87% of whom were male in this sample).[371] Another study conducted with Hispanic PLWH (60% of participants were male) compared the IPAQ short form with accelerometer and pedometer data, observing a correlation coefficient of 0.76 between pedometer steps per day and IPAQ minutes per week.[372] Furthermore, accelerometer-measured physical activity levels were lower than those estimated by the IPAQ, providing further evidence that physical activity monitors measure physical activity levels more accurately than self-reported questionnaires in this population.[372]

The RAPA questionnaire[373] has emerged as a useful self-reported physical activity questionnaire for measuring regular moderate-intensity physical activity among older adults.[374] It was originally validated with healthy older adults aged 50 and older and consists of 9 items to assess physical activity levels using two different scores: RAPA 1 indicates the level of aerobic physical activity and RAPA 2 indicates participation in resistance and flexibility activities.[373] The RAPA has been used increasingly to estimate physical activity levels in the HIV population.[361,375,376]

The RAPA has a strong association with other short self-reported physical activity measures such as the Behavioral Risk Factor Surveillance System (BRFSS) questionnaire, the Patient-centered Assessment and Counseling for Exercise (PACE), and the Community Healthy Activities Model Program for Seniors (CHAMPS).[373] The RAPA also has as good or better sensitivity (81%), positive predictive value (77%), and negative predictive value (75%) for measuring physical activity among older adults relative to the aforementioned self-reported measures of physical activity.[373] In contrast, a study conducted with 66 older female adults in Mexico determined that the RAPA did not accurately measure physical activity levels when compared with accelerometers.[374] However, because a small sample size was used in the study, the investigators chose to classify individuals using a dichotomous variable (exercises or non-exercisers).[374]

Accelerometers are the gold standard for measuring physical activity levels among older adults.[374] A recent scoping review conducted by Dagenais and colleagues (2019) characterized the use of wireless physical activity monitors among PLWH, determining that accelerometers and pedometers are increasingly being used to measure steps taken per day, distance walked, and the number of physically active minutes.[377] A cross-sectional study by Ramirez-Marrero (2008) which evaluated steps per day using pedometers determined that male PLWH took 7,594 steps per day on average and female PLWH walked 7,151 steps per day on average.[372] In the same study, the authors also used accelerometers, observing that male PLWH took a mean of 7,495 steps and female PLWH walked 7,886 mean steps per day.[372] Comparatively, a meta-analysis of 24 studies conducted by Vancampfort and colleagues (2018) determined that PLWH take only 5,899 steps per day on average, using objective methods of data collection.[362] A possible explanation for the discrepancy in step counts observed among PLWH is that Vancampfort and colleagues (2018) used a trim and fill analysis which excludes small studies in order to form a symmetrical plot and estimates an adjusted effect including only the large studies. Furthermore, the study by Vancampfort et al. (2018) included older adults, while the participants in the cross-sectional study by Ramirez-Marrero (2008) did not. Indeed, the meta-analysis by Vancampfort et al., (2018) determined that older age was a moderator of steps walked per day.[362] It is also important to note that Ramirez-Marrero and colleagues (2008) noted that PLWH in their sample significantly over-estimated their physical activity (as measured using the IPAQ) compared to accelerometers (339.5 versus 143.5 minutes/week in moderate-vigorous physical activity, respectively).[362] In general, like HIV-negative individuals, PLWH tend to overestimate moderate and vigorous intensity activity and underestimate light activity and sedentary time.[362] While accelerometers are useful measures of aerobic exercise, they may be less sensitive to non-aerobic activities such as resistance training.[378]

Health-Related Quality of Life

Quality of life is defined by the World Health Organization as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards, expectations and concerns."[379] HRQoL is a multi-dimensional concept that includes physical, mental, emotional, and social function domains.[380] Both quality of life and HRQoL are affected in this population, but the focus of this section will be mainly on HRQoL.

PLWH have considerably lower HRQoL than the general population, even among those who are virologically and immunologically stable.[381] When compared with other chronic conditions, the odds of poor physical HRQoL among PLWH are comparable with individuals with diabetes, and are lower than individuals with rheumatoid arthritis.[382] Further, poor mental HRQoL is more likely among PLWH than other chronic conditions.[382] AIDS history, longer cART duration, and severe comorbidities are associated with worse physical HRQoL among PLWH.[382] Fatigue is also associated with lower HRQoL among PLWH, even among individuals with mild fatigue.[383] Social factors such as social isolation, relationship difficulties, and stigma can also impact HRQoL among PLWH.[384] Gender appears to be an important predictor of HRQoL among PLWH. A cross-sectional study conducted in Ethiopia with 520 PLWH determined that women had significantly lower HRQoL than men in four domains.[385] A cross-sectional study conducted in India with 120 PLWH revealed similar findings; male PLWH had higher HRQoL in five domains compared to females, and their multivariate analysis revealed that female gender was associated with lower HRQoL in their sample.[386]

There are several factors associated with better HRQoL in the HIV population. Lower viral load, higher CD4+ count,[387] and fewer or less severe HIV symptoms[388] are associated with better HRQoL among PLWH. Individuals with better cART adherence and those taking fewer pills also have better HRQoL.[387,389]

Quality of Life Measures

Many HRQoL instruments have been used to measure well-being among PLWH. A systematic review of 10 reviews evaluating HRQoL measures among PLWH concluded that the EuroQol Five Dimensions Questionnaire (EQ-5D), Short Form-36 (SF-36), World Health Organization Quality of Life (WHOQOL-BREF), and Medical Outcomes Survey-HIV (MOS-HIV) were commonly used in the literature and had the best psychometric properties.[390] The EQ-5D measures five aspects of HRQoL (mobility, self-care, usual activities, pain and discomfort, anxiety and depression) and takes only one minute to complete.[391] The questionnaire also includes a perceived health status VAS ranging from 0 to 100.[391] However, it is susceptible to ceiling effects and is not recommended for use with asymptomatic PLWH.[392,393]

As the name suggests, the SF-36 comprises 36 items which make up 9 domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, and health transition) and takes 10 minutes to administer.[390] The SF-36 appears to be sensitive to cART initiation, changes in CD4+, viral load and HIV symptomology, but may not be responsive to changes in cART among PLWH who are on a stable regimen.[392–394]

The WHOQOL-BREF consists of 26 items covering 4 domains: physical health, mental health, social relationships, and environment with higher scores indicating better

HRQoL.[395] The original instrument (the WHOQOL-100) consisted of six domains, but factor analysis determined that the physical subscale should be merged with the independence subscale, and the psychological subscale should be merged with the spirituality, religion, and personal beliefs subscale to create the abbreviated version with 4 domains.[396] The instrument takes less than 5 minutes to complete, is associated with HIV severity and CD4+ count, and is a reliable HRQoL measure.[379,393–395]

The World Health Organization also developed versions of the WHOQOL-100 and the WHOQOL-BREF specifically for PLWH; the WHOQOL-HIV and the WHOQOL-HIV BREF, respectively. Like the WHOQOL-100, the WHOQOL-HIV has 6 domains, but there are additional HIV-specific questions such as HIV symptoms under the physical domain; social inclusion under the social relationships domain; and forgiveness and blame, concerns about the future, and death and dying under the spirituality/religion/personal beliefs domain for a total of 120 items.[393] The WHOQOL-HIV BREF has 31 items and contains five additional items specifically for PLWH (one regarding physical HIV symptoms, one regarding social inclusion, and one each regarding blame, fear for the future, and death) preserving the original 6 domains from the WHOQOL-100.[397] The WHOQOL-HIV BREF has good internal consistency, reliability, and discriminant validity for those at different stages of HIV disease.[397]

The Functional Assessment of HIV (FAHI) is an HIV-specific 47-item HRQoL questionnaire that includes five domains: physical, emotional, social, and cognitive quality of life, and functional and global well-being.[398] According to a review on quality of life measures used with the HIV population, the FAHI is recommended for use in international clinical trials.[392] A study evaluated the psychometric properties of the FAHI among two large samples of PLWH and discovered that most items had acceptable convergent and discriminant validity; but changes in FAHI scores were not associated with viral load changes.[399]

The MOS-HIV is the most commonly used HRQoL measure in the HIV population and consists of 35 items encompassing 11 domains: general health, physical function, pain, social function, role function, emotional well-being, energy/fatigue, cognitive function, health distress, quality of life, and health transition.[400] It takes approximately 5-10 minutes to administer.[400] Among HIV-specific measures, the MOS-HIV has the most well-established psychometric properties.[390] It appears to have good internal consistency, construct validity, and acceptable convergent and discriminant validity.[392–394] The MOS-HIV is responsive to adverse events, changes in symptoms, opportunistic infections, AIDS-defining events, and cART initiation.[390,392,394] Despite this, a ceiling effect may be present on the cognitive functioning, pain, and health transition domains of the instrument among individuals with advanced HIV.[393,401]

Mental Health

Depression

Mental health concerns are common among PLWH and can have an effect on HRQoL, cART adherence, and HIV progression.[402–405] Among PLWH, depression rates are two to three times higher than the rates observed among HIV-negative individuals.[406–408] A review of cross-sectional and longitudinal studies estimated that the prevalence of depression among PLWH (70% of whom were male) ranged from 6 to 41% (median = 24.6%), the prevalence of current major depressive disorder ranged from 20 and 27% (median = 24.2%), and lifetime major depressive disorder ranged from 26 to

50% (median = 42%).[409] Many factors are thought to contribute to the high rates of depression among PLWH, including HIV diagnosis, living with a chronic condition, loneliness, and stigma.[410] There is also a high prevalence of psychosocial and behavioural risk factors for depression such as trauma in early life, exposure to violence, financial instability, reduced healthcare access, lack of education, substance and alcohol use, and unemployment.[406,411] Mental health concerns can affect viral suppression; a retrospective study determined that PLWH with mental health diagnoses were less likely to attain viral suppression than those without mental health diagnoses.[412] Finally, female gender predicted the presence of major depression among PLWH living in South Africa.[413]

Anxiety

Relative to other mental health conditions such as depression, anxiety disorders among PLWH are understudied. Depending on the type of assessment, the rates of anxiety disorders in this population can vary. A critical review published in 2017 determined that diagnoses of anxiety disorders were significantly higher when questionnaires were used (33% of PLWH) relative to a traditional interview (23% of PLWH).[414] Compared to the general population, PLWH experience higher rates of anxiety disorders (18% vs 23%, respectively).[414,415] Regarding individual anxiety disorders diagnosed using diagnostic interviews, there is a similar trend, with 10% of PLWH experiencing panic disorder relative to only 3% in the general population), generalized anxiety disorder (which affects 6% of PLWH compared to 3% in the general population), and social anxiety disorder (9% compared to 6%).[414] Of note, anxiety and depression severity is higher among female PLWH compared to men.[416]

The available literature indicates that anxiety disorders can have an effect on health-related quality of life, drug use, cognitive performance, and cART non-adherence. A study conducted with PLWH (64% male) in Ireland with a history of intravenous drug use determined that anxiety disorders predicted HRQoL.[417] Staton-Tindall et al. (2015) observed a relationship between anxiety symptoms and elevated injection drug use among incarcerated female PLWH.[418] A longitudinal study has concluded that cognitive performance over 18 months was significantly lower among male PLWH with anxiety symptoms; but the sample consisted of only 30 PLWH.[419] Finally, a prospective study of 1,910 PLWH determined that generalized anxiety disorder and panic disorder were associated with cART non-adherence a year later.[31]

Mental Health Outcome Measures

The Structured Clinical Interview for DSM-IV (SCID) is considered the gold standard for identifying and characterizing mental disorders.[420] However, interviews are often not clinically feasible,[421] and few studies have evaluated their psychometric properties.[422] A systematic review determined that the sensitivity of the SCID is 85% and the specificity was 92% among HIV-negative inpatient and community-dwelling individuals.[422]

The Center for Epidemiological Studies-Depression (CES-D) scale is one of the most common screening instruments used in HIV research.[423,424] It consists of 20 self-reported items where participants rate the frequency of symptoms in the past week on a 4-point scale with scores above 16 indicating a high level of depressive symptoms.[423] The CES-D has good reliability and validity across many different populations.[425,426] Gay and colleagues (2018) recently performed a Rasch analysis using data from a diverse sample of 347 adult PLWH (231 males, 93 females, 23 transgender) and determined that the CES-D had acceptable internal consistency but lacked internal validity, and had poor generalizability to individuals with different genders, races, or an AIDS diagnosis.[426]

The Patient Health Questionnaire-9 (PHQ-9) is a brief self-administered or interviewer-administered instrument that measures both depression severity and diagnoses.[427] Scores for the PHQ-9 range from 0-27, with scores of 0-4 indicating minimal depression, 5-9 indicating mild depression, 10-14 describing moderate depression, 15-19 indicating moderately severe, and 20–27 describing severe depression.[427] A study conducted in the United States concluded that the PHQ-9 demonstrated superior diagnostic accuracy for depression than health care provider reports.[428] In contrast, a quasi-experimental study of adult PLWH determined that only 74% of PLWH who screened positive for depression using the PHQ-9 had the diagnosis confirmed using the gold standard SCID.[429]

The profile of mood states (POMS) was developed in 1971 and originally consisted of 65 items.[430] More recently, an abbreviated 30-item version was developed.[431] The POMS consists of six subscales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.[432] Participants rate items on a 5-point Likert scale ranging between “not at all” to “extremely.”[432] The POMS has not been well studied among PLWH,[433,434] but has been shown to have strong concurrent and discriminant validity, as well as very good retest reliability and excellent internal consistency of the subscales among HIV-negative older adults.[435]

The Beck Depression Inventory (BDI) was developed in 1961 and originally consisted of 21 questions,[436] then was adapted and renamed to the BDI-II in 1996 due to changes in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition.[437] Similar to the BDI, the BDI-II contains 21 questions, each response is scored on a scale of 0-3, and higher scores indicate more severe symptoms of depression.[438] Scores of 0-13 indicate minimal depression, 14-19 indicate mild depression, 20-28 indicate moderate depression, and 29-63 indicate severe depression.[438] The instrument takes between 5-10 minutes to self-administer and 15 minutes to be administered in interview format.[438]

The BDI and BDI-II have been used to measure depression in studies with PLWH.[439] A CHARTER study determined that BDI-II scores among PLWH demonstrated good internal consistency (Cronbach's alpha=0.93) and adequate test-retest reliability (Intraclass correlation=0.83) over six months, and the authors concluded that the BDI-II is an adequate measure of depression among PLWH in the United States.[440] Measuring anxiety and depression among PLWH can be challenging, due to the overlap between physical symptoms of HIV (such as fatigue and insomnia) and mental health symptoms.[439,441] One study discovered that higher depression scores (measured using the BDI) were observed among PLWH who were symptomatic than those who were asymptomatic.[439] These results were likely due to the influence of somatic items on the BDI, as affective scores were not different between asymptomatic and symptomatic individuals.[439]

Similar to the BDI, the Beck Anxiety Inventory (BAI) is a self-report questionnaire with 21 items in which the participant rates the severity of anxiety symptoms in the past week.[442] A score above 10 on the BAI indicates mild anxiety symptomology, while a score above 19 indicates moderate anxiety.[443] A study conducted in South Africa among 101 PLWH (82% were female) receiving cART treatment determined that the BAI had high internal consistency (Cronbach's alpha = .89), and higher order factor analysis determined that the BAI is a valid measure in this population.[444]

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report questionnaire with anxiety and depression subscales.[445] Scores of 0-7 in each subscale indicate normal anxiety and depression, scores of 8-10 are considered borderline, and 11 or over indicating anxiety or depression symptoms.[445] The HADS has excellent test-retest reliability and internal consistency, very good convergent validity, and acceptable discriminant validity according to a study of 162 French-Canadian PLWH (91% male).[441] When compared with the BDI, HADS scores appear to be less susceptible to HIV symptom confounds among PLWH.[441] Due to its simple and fast administration, Savard and colleagues (1998) recommended the HADS be used in routine clinical care with PLWH.[441]

Chapter 5-Exercise and Cognitive Function in People Living with HIV: A Scoping Review

This chapter is a manuscript that was published in *Disability and Rehabilitation* in January 2018. The article maps the available literature on exercise and physical activity among PLWH.

Copyright Statement

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Contribution Statement

I searched for articles with the help of Robin Parker. Along with Dr. Kelly K. O'Brien, we searched article titles and abstracts for articles for inclusion. I also extracted information from the included articles, drafted the manuscript, and received edits from the co-authors.

Abstract

BACKGROUND: Since the advent of antiretrovirals, people with HIV are living longer and have improved quality of life. However, 30-60% of these individuals experience cognitive impairment. Fortunately, physical activity has emerged as a management strategy for cognitive impairment. Purpose: To map the evidence on physical activity and cognition in HIV. METHODS: We searched 5 databases using terms related to physical activity and HIV. Two authors independently reviewed titles and abstracts for studies that addressed physical activity/exercise and cognition in people with HIV. Authors reviewed full texts to identify articles that met our inclusion criteria. One author extracted the data, then we collated the results and summarized the characteristics of included studies. RESULTS: Sixteen studies from high-income countries were included; eight were interventional (five randomized controlled trials and three pre-post single group observational studies) and eight were non-interventional studies. The interventional studies included aerobic, resistive, and Tai-Chi exercise for 8 weeks to 12 months in duration. Two of eight interventional studies found exercise to benefit self-reported cognition. All eight non-interventional studies showed a positive relationship between physical activity and cognitive function. CONCLUSION: Results of this study suggest that physical activity may preserve or improve cognition in people living with HIV.

Keywords: AIDS, rehabilitation, cognition, physical activity, aerobic exercise, resistive exercise

Introduction

HIV (*Human Immunodeficiency Virus*) is a chronic condition[446] affecting 36.9 million people worldwide.[447] Since the introduction of combination antiretroviral therapy, quality of life and life expectancy have improved for people living with HIV.[67] Nonetheless, they continue to experience significant challenges, including cognitive dysfunction.[67,138] In fact, there has not been a dramatic decrease in cognitive impairment since the advent of combination antiretroviral therapy[67] - inflammatory markers associated with cognitive decline remain present in those with stable HIV infection.[448] The reported prevalence of cognitive impairment varies in the HIV population between 30-60%, depending on the stage of infection.[74,449]

This cognitive impairment, also known as HIV-associated neurocognitive disorders, can be classified as follows: 1-asymptomatic neurocognitive impairment, which has an estimated prevalence of 33%; 2-mild neurocognitive disorder, which has a prevalence of 12%; and 3-HIV-associated dementia, with a 2% prevalence.[47] Cognitive dysfunction is more prevalent among older adults living with HIV,[112] and the number of older adults with HIV is expected to grow as the general population ages and people become infected with HIV later in life.[450]

HIV infection can have a significant impact on the structure and function of the brain. The virus can weaken the blood-brain barrier, allowing entry of inflammatory cytokines and other neurotoxins.[451] HIV does not affect the neurons directly, but rather attacks microglial cells, causing neuro-inflammation.[451] In addition, cardiovascular comorbidities may contribute to depletion of cognitive reserve.[451]

Cognitive symptoms associated with HIV infection include deficits in attention, learning, memory, motor coordination, and processing speed.[110] These cognitive concerns have significant real-world consequences in terms of employment, medication adherence, and driving.[57] People with HIV experience 2-3 times the unemployment rate of their HIV-negative counterparts;[452] and those who remain employed are five times more likely to report difficulty managing work demands.[57,453] Cognitive performance is an important predictor of adherence to medication,[78,454] which is vital to maintaining immunological function, decreasing viral load, and improving cognition.[57] Non-pharmacological strategies to address sequelae related to cognitive deficits are needed.

Exercise has recently emerged as an effective management strategy for cognitive impairment in the general population. Three systematic reviews have drawn clear links between regular physical activity and cognitive preservation in those without disability.[455–457] The earliest review, involving 16 prospective studies, reported that engagement in high levels of physical activity reduced the likelihood of dementia and Alzheimer's disease by 28% and 48%, respectively, compared to low levels of physical activity.[455] A more recent systematic review and meta-analysis of 25 randomized control trials of older adults concluded that participation in physical activity improved measures of reasoning, attention, and processing speed compared to control interventions.[456] The third review and meta-analysis with 79 studies showed meaningful improvements in cognitive ability during exercise, immediately afterward, and following a delay, with aerobic and multimodal exercise yielding the greatest benefits.[457]

Exercise is also an effective strategy for managing cognitive decline in chronic disease. A 2012 systematic review of 12 randomized controlled trials on the effects of physical activity on cognitive function in patients post-stroke provided evidence that physical activity-based interventions had a significant positive effect.[458] Another systematic review of six randomized controlled trials and one controlled clinical trial concluded that aerobic exercise resulted in improvements in overall cognition of people with dementia, choice reaction time of people with multiple sclerosis, and motor learning skills of individuals post-stroke.[459]

While the effects of exercise on cognitive function in both clinical and non-clinical populations have been investigated using rigorous study designs, much of the evidence on exercise and cognition in HIV has been derived from cross-sectional studies. Despite design limitations, the knowledge generated to date provides valuable insights for clinical practice, future research, and policy on this important topic. Thus, we set out to conduct a scoping review to map the evidence regarding the role of physical activity on cognition in people living with HIV. A scoping review was selected because it affords a comprehensive review of the literature without restrictive inclusion criteria regarding study design or quality.[460] This approach is appropriate for a newly emerging inquiry into the interaction of physical activity and cognition in the context of HIV. In addition, such a review is useful in determining the potential value and scope of a future systematic review.

Methods

The structural framework used in this scoping review was developed by Arksey and O'Malley,[461] which was further expanded and clarified by Levac, Colquhoun, and O'Brien.[460] The framework consists of six stages: identifying the research question; searching for relevant studies; selecting studies for inclusion; charting the data; collating, summarizing, and reporting the results; and consulting stakeholders.[461]

Consulting Stakeholders

Although stakeholder consultation is the last stage of the Arksey and O'Malley framework, we addressed it first. We consulted five members of the community (two people with HIV and three HIV health care providers) regarding their perspectives on the role of physical activity in moderating cognitive impairment in people living with HIV. This consultative process reinforced the need to assess existing evidence on this topic and helped shape the research question.

Identifying the Research Question

Our research question was "what is known about the role of physical activity in enhancing cognition in people living with HIV?" The principal topics of interest were the parameters of exercise interventions; tools to assess cognition and physical activity; associations between physical activity and cognition; and effectiveness of exercise interventions.

Searching for Relevant Studies

Searches were conducted by the reference librarian, using Embase (Elsevier), MEDLINE (Ovid), CINAHL (EBSCO), PsycINFO (EBSCO), and SportDiscus (EBSCO) databases. Reference lists of the relevant studies and reviews were also hand-searched to ensure comprehensive coverage of the topic. Search terms included synonyms, index terms, and variant phrases of exercise and physical activity together with various terms to capture the concept of HIV (Table 1). Covidence, an online software program, was used to upload search results.[462]

Table 1: Sample search strategy (MEDLINE)

1.	Ch'i Kung.tw.
2.	qigong.tw.
3.	dance therapy.tw.
4.	pilates.tw.
5.	tai chi.tw.
6.	yoga.tw.
7.	mind body.tw.
8.	exp Exercise Therapy/
9.	exp Exercise/
10.	exp Sports/
11.	physical therapy modalities/ or exp exercise movement techniques/
12.	qigong/ or tai ji/ or yoga/
13.	("Tai Chi Chuan" or Taijiquan or "T'ai Ch'i Ch'uan" or Qigong or "Chi Gung" or "Chi Gong" or "Chi Kung").tw.
14.	running.tw.
15.	walk*.tw.
16.	jogging.tw.
17.	swim*.tw.
18.	physical conditioning.tw.
19.	(dance or dancing).tw.
20.	resistance training.tw.
21.	(exercise* or exercising or exercize* or exercizing).tw.
22.	aerobics.tw.
23.	aerobic fitness.tw.
24.	physical activit*.tw.
25.	or/1-24
26.	exp HIV/
27.	exp HIV Infections/
28.	AIDS-Related Opportunistic Infections/
29.	acquired immune deficiency syndrome.tw.
30.	hiv.tw.
31.	"hiv/aids".tw.
32.	aids related.tw.
33.	Human immunodeficiency virus.tw.
34.	aids virus*.tw.
35.	or/26-34
36.	25 and 35

Selecting Studies to Include

Peer-reviewed articles published in English between January 1, 1996 and September 18, 2017 that also (i) investigated some form of physical activity or exercise (*physical activity* was defined as any bodily movement produced by skeletal muscles that results in energy expenditure and *exercise* as planned, structured, and repetitive physical activity that aims to improve or maintain physical fitness[463]), (ii) reported data separately for people with HIV, and (iii) measured cognitive outcomes using quantitative neuropsychological assessment, self-report, or both were included.

Two reviewers independently screened titles and abstracts. Both reviewers subsequently reviewed all potentially relevant articles to identify those that met the inclusion criteria. In the event of disagreements, a third reviewer was consulted to determine final study inclusion.

Charting the Data

We extracted data from the included articles using a chart extraction form with columns for the research question(s), study design, participant characteristics, cognitive measure(s), intervention or subgroup comparison, and main findings. Although quality assessment of included studies is not a necessary component of scoping review methodology, we used the Physiotherapy Evidence Database Reported Outcomes (PEDro) scale to assess the quality of randomized controlled trials on a scale of 0-10,[464] with 9-10 considered “excellent” quality; 6-8, “good”; 4-5, “fair”, and <4, “poor” quality.[465] Items of the Physiotherapy Evidence Database Reported Outcomes scale include: eligibility criteria, random allocation, allocation concealment, group similarity at baseline, subject blinding, therapist blinding, assessor blinding, measures of at least one key outcome obtained from more than 85% of the subjects, intention to treat analysis, between-group statistical comparisons, and point measures and measures of variability.[466] The score is calculated by counting the number of aforementioned items that have been satisfied, except eligibility criteria, which is not included in the score.[466] It is important to note that in exercise interventions, participant and exercise instructor blinding is not possible; therefore, the maximum possible score is 8 in these types of studies.

Collating, Summarizing and Reporting the Findings

Studies were classified as interventional or non-interventional to facilitate summarizing the findings. Interventional studies with a qualitative component pertaining to cognitive outcomes were thematically analyzed, as per Levac, Colquhoun, and O'Brien.[460] The results were collated and summarized for reporting purposes using the following headings: study designs; participant descriptions; methodological quality; parameters of exercise interventions; assessment tools for cognition, physical fitness and physical activity/exercise; associations between physical activity/exercise and cognition; and effectiveness of exercise interventions.

Results

Study Designs

The initial searches yielded 10,016 articles for possible inclusion in the scoping review (Fig. 1). Sixteen studies that met the inclusion criteria were included – five randomized controlled trials,[434,467–470] three pre-post single group observational studies,[471–473] and eight cross-sectional studies.[150–157] One investigation was described by the authors as a randomized controlled trial but because data collection was limited to the experimental group, it was reclassified as a single group pre-post intervention study. Eight studies were classified as interventional (Table 2) and eight as non-interventional studies (Table 3).

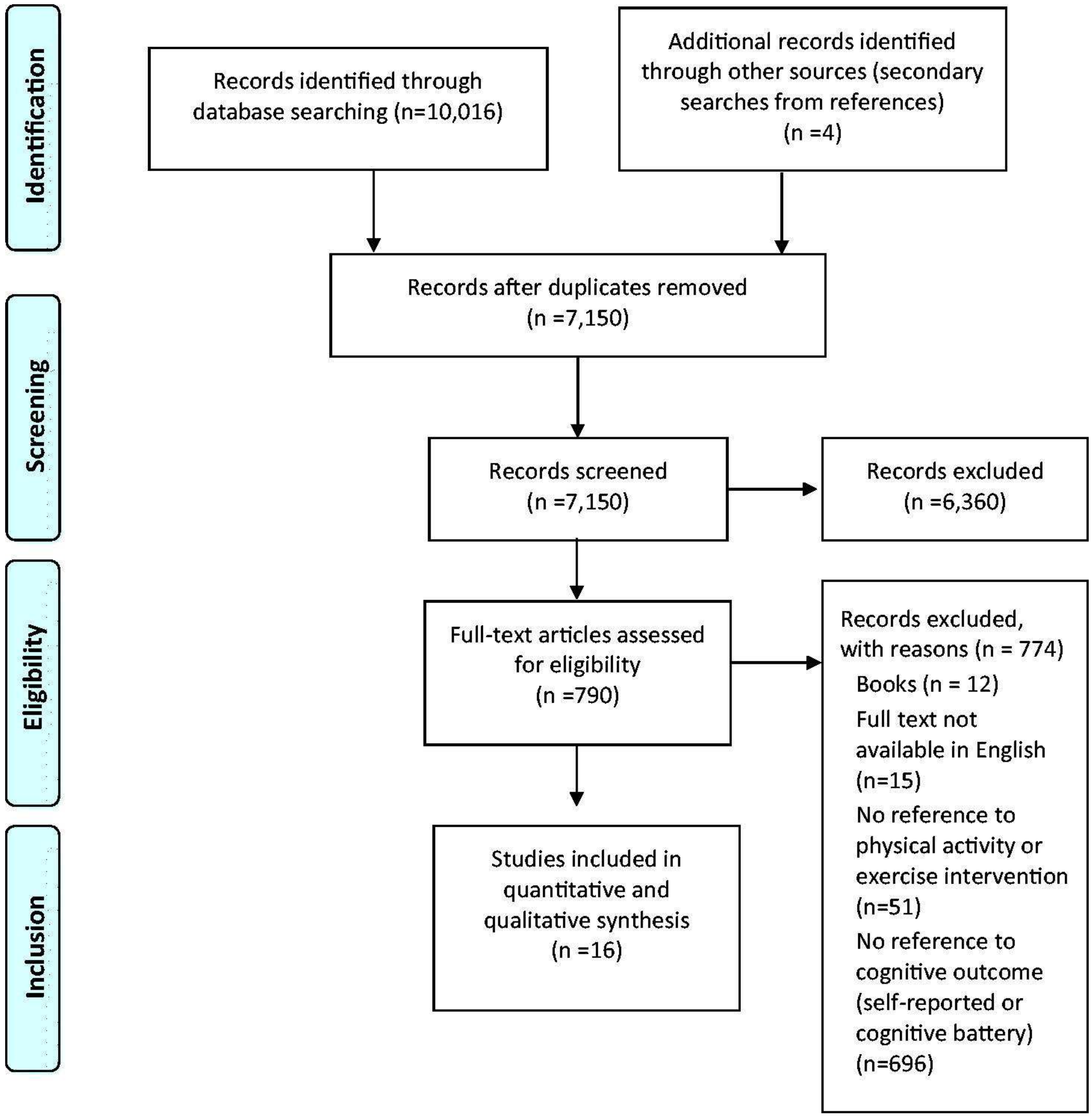

Figure 1: Flow chart for study selection

Participant Descriptions

A total of 1,701 participants with HIV were involved in the 16 included studies - 383 in interventional studies (mean, 48 participants/study; range, 11-99) and 1,318 in non-interventional studies (mean, 165 participants/study; range, 37-335). Included studies were conducted in the United States of America, United Kingdom, and Australia and published between 1997 and 2017.

In the interventional studies, the mean age of the participants was 42.4 years, and 82% were male. Two studies included only asymptomatic people with HIV,[467,468] one study involved only people with AIDS (Acquired Immunodeficiency Syndrome)[434] [defined by the Centers for Disease Control[19] as T Lymphocyte count (also known as the CD4 count) of <200 cells/mm or the presence of an AIDS-defining illness], two had a combination of participants with HIV and AIDS,[471,473] and three others did not report stage of infection.[469,470,472] Four of the interventional studies excluded participants if they had significant cognitive impairment.[434,469–471] In all included randomized controlled trials, there were no significant differences between groups in cognitive outcomes at baseline.[434,467–470] Baseline demographic characteristics were similar between control and interventional groups in three of the included randomized controlled trials;[434,468,469] however, one study stated that the exercise group was significantly older than those in the control group,[467] and another did not state the statistical differences in demographic information between groups at baseline.[470]

Table 2: Interventional studies included in the review (n=8)								
Author, year, setting, design	**Participants**	**Cognitive measures**	**Fitness/PA measures**	**Intervention(s)**	**Supervision**	**Adherence**	**Cognition-related findings**	**PEDro score**
Baigis et al. 2002 USA Home-based RCT	n=99 Mean age: 37y 80% male 100% asymptomatic 0% on cART VL: NR CD4=358.2	MOS-HIV-cognitive subscale	$V0_{2max}$	15 wk of 20-min aerobic exercise 3x/wk for (75-85% HR_{peak}[b] (Total dose=15 h) vs control (no exercise)	Nurse or trainer	83% at 15 weeks in exercise group	MOS-HIV: No change in cognitive subscale scores (p=.86)	5/10
Fillipas et al. 2006 Australia Hospital or community gym RCT	n=40 Mean age: 44 y 100% male % AIDS: NR 62.5% on cART VL: 68.05 CD4: 461	MOS-HIV-cognitive subscale	Kasch Pulse Recovery Test	6 mo of 1-h aerobic (60-75% HR_{max}) and resistance exercise (60-80% 1RM) 2x/week (Total dose=52 h) vs control (20-min walking sessions 2x/wk)	Physical therapists	Participants in treatment group attended 81% of exercise sessions	MOS-HIV: Exercise group improved 14 points over controls (*p*=.04)	8/10
Galantino et al. 2005[a] USA Outpatient infectious diseases clinic RCT	n=38 Mean age: 39y 100% male 100% AIDS 100% on cART VL, CD4: NR	MOS-HIV-cognitive subscale POMS-confusion bewilderment subscale	Functional tests (sit-up test, stair climbing, Physical Performance Test)	8 wk of 1-h class 2x/wk of Tai Chi vs strength and endurance (<60-70% $HR_{reserve}$) exercise (Total dose=16 h) vs control (no exercise)	Tai Chi instructor and physical therapist	Tai Chi group more adherent than comparison groups	MOS-HIV and POMS: No significant group differences (p=.46) Some positive qualitative changes in exercise groups related to cognition	3/10
Gillespie 1997 USA Rehabilitation center RCT	n=23 Mean age: 36y 91% male 100% asymptomatic % on cART: NR VL: NR CD4: 344	MOS-HIV-cognitive subscale	None	12 wk of 1-h aerobics (60-80% $V0_2$peak) 3x/wk (Total dose=36 h) vs control (no exercise)	Exercise trainer	"completers" (n=18, 78%), and "non-completers" (n=5, 22%)	MOS-HIV: No significant group differences (p=.494)	4/10
McDermott et al. 2017 Ireland St. James' Hospital RCT	n=11 Mean age: 43.5 73% male % with AIDS, cART use, VL, CD4: NR	MoCA, Trails A and B	Aerobic fitness (modified Bruce protocol), seven day accelerometry	16 wk aerobic exercise, 3 times per week vs control (no intervention) for 31-52 (avg=46) minutes at 40-75% HRR or 12-16 Borg Scale (avg total dose=37h)	2 sessions supervised by physical therapists, 1 session unsupervised	60% adherence to exercise sessions. (68% adherence to unsupervised sessions, 56% to supervised sessions)	Baseline; higher levels of moderate PA were positively correlated with higher MOCA scores (P = 0.04). Higher aerobic fitness was negatively correlated with Trail A scores (P = 0.001). Exercise training= no change in MoCa scores, p=.32, Trails A, p=.8, Trails B, p=.91)	5/10
Brown et al. 2016 UK Outpatient hospital Pre-post single cohort	n=92 Mean age: 52y 82% male % AIDS,% on cART, VL, CD4: NR	FAHI-cognitive subscale	6-minute walk test	10 wk of 1-h moderate to vigorous exercise (aerobic, neuromotor, resistive:70% 1RM, 1-3 sets, 8-15 reps) 2x /wk (Total dose=20 h)	Physical therapists	46% of participants attended ≥8/20 sessions	FAHI: No change in cognitive subscale scores (p=.635)	NA
Robins et al. 2006 USA Setting NR Pre-post single cohort	n=59 Mean age: 42y 59% male 48% AIDS % on cART: NR VL, CD4: NR	FAHI-cognitive subscale	None	10 wk of 1-h Tai Chi 1x/wk (Total dose=10 h)	Not stated	NR	FAHI: Significant pre-post change (p=.042) in cognitive subscale.	NA
Schlabe et al. 2017 Germany Setting NR Pre-post single cohort	n=21 (13 completed) Mean age: 42 92% male 23% AIDS history CD4: 620 85% on cART 82% undetectable VL	MOS-HIV-cognitive subscale at 4 time points before and during training	None	Progressive aerobic training, 3-10 hr/week (3-4 weekly sessions) at 60–80% of HR_{max}, and sprints for 12 months vs HIV+ reference group, gathered longitudinal data on interventional group only	Exercise scientists	13/21 (62%) completed marathon. Adherence to sessions NR	No change in MOS-HIV cognitive subscale scores (p>.05)	NA

PA: physical activity; RCT: randomized controlled trial; y: years; cART: Combination Antiretroviral Therapy; VL: viral load MOS-HIV; HR_{peak}: peak heart rate; min: minutes; h: hours; wk: week(s); Medical Outcome Survey-HIV, VO_{2peak}: maximal oxygen consumption; POMS: Profile of Mood States; HR_{max}: maximal heart rate; 1-RM: one resistance maximum; MoCA: Montreal cognitive assessment: FAHI: Functional Assessment of HIV Infection; reps: repetitions; NA: not applicable. [a]Main article was Galantino et al.,[434] supplemented by Galantino et al.[474] [b]Recorded during stress tests.

Mean age in non-interventional studies was 48.0 years, and 82% were male. One study involved only asymptomatic individuals with HIV,[157] one involved only people without AIDS,[156] four included mostly participants with AIDS,[150,151,154,155] one had very few participants with AIDS,[153] and one did not report stage of infection.[152] All non-interventional studies used objective measures of cognitive impairment, and two categorized participants as having HIV-associated cognitive disorder.[150,156] Each of the cross-sectional studies adjusted for possible confounders, such as age, gender, T-Lymphocyte count, viral load, AIDS status, substance use, and education. (Table 3)

Table 3 Cross-sectional studies included in the review (n=8)

Author Country	Participants	Cognitive Measures or Outcomes	Fitness PA measures	Group comparisons	Confounders included in analysis	Cognition-related findings
Dufour et al. 2013 USA	n=335 Mean age: 48y 77% male 64.7% with AIDS 82.2% on cART VL: 30% undetectable CD4: 540	Cognitive battery: Verbal fluency, working memory, processing speed, learning and recall, executive function, motor function	Self-report of PA over past 72 h	2 subgroups: Exercisers versus non-exercisers	Demographic factors, HIV disease (CD4, AIDS), substance use, depression, mental health status, and physical functioning	Exercisers had lower global cognitive impairment (OR= 2.63, $p < .05$), specifically working memory ($p<0.05$) and processing speed ($p<0.05$).
Dufour et al. 2016 USA	n=235 Mean age: 49.2 73% male 63% with AIDS 85% on cART 73% undetectable VL 14.9 years with HIV CD4: 542	Cognitive battery: verbal fluency, working memory, speed of information processing, learning, memory, executive function, and motor function	Self-report of PA over past 72 h	3 subgroups: No PA, inconsistent PA, and consistent PA	Age, ethnicity, gender, education, PA group, HIV cerebrospinal VL	Better global cognitive scores in consistent PA group than the no PA ($p< 0.001$) and the inconsistent PA group ($p<0.01$). Better verbal fluency, executive function, speed of information processing, and working memory in consistent PA group vs other groups ($p<.05$)
Fazeli et al. 2014 USA	n=139 Mean age: 49 y 80% male 66% AIDS 46% with HAND 87.6% on cART VL: 66% undetectable CD4: 551	Cognitive battery: Verbal fluency, working memory, processing speed, verbal and visual learning, delayed recall, executive function, motor function[a]	Active Lifestyle Factors (ALFs) Questionnaire of PA over past 72 h	0, 1, 2, 3 Active Lifestyle Factors (exercise, social activity, employment)	Age, gender, education, IQ, ethnicity, HIV disease characteristics (CD4, AIDS status, ART use, and viral load), substance use, depression	Positive association between ALFs and global cognitive performance (OR=.64, p=.01,), and specifically verbal, executive function, speed of information processing, recall, and working memory ($p<.05$)
Fazeli et al. 2015 USA	n=100 Mean age: 58y 88% male 66% AIDS 98% on cART VL: 92% undetectable CD4: 597	Cognitive battery: Verbal fluency, working memory, processing speed, verbal and visual learning, delayed recall, executive function, motor function[a]	IPAQ Short Form	3 subgroups: low, moderate, and high PA levels based on IPAQ	Age, gender, education, ethnicity, HIV disease characteristics (duration of HIV, CD4, AIDS status, cART use, viral load, substance use, depression	Higher levels of moderate PA were associated with lower odds of NCI (OR=0.94, p=.01), specifically executive function (p=.04).
Honn et al. 1999 USA	n=139 Mean age: 33y 100% male 100% asymptomatic % on cART, VL, CD4: NR	Cognitive battery: WAIS-R, Wisconsin Card Sorting Test, Verbal Concept Attainment Test, Trail Making Test A/B, Visual Span (Forward/Backward), Grooved Pegboard Test, Verbal Fluency Test, Figural Fluency Test, PASAT, Selective Reminding Test, reaction time	Self-report of exercise using 2 closed questions	2 subgroups: exerciser vs inactive based on self-reported questionnaire prior to findings of seropositivity	Education, marijuana disorder, stratified by current exercise participation	Exercisers scored higher on Grooved Pegboard Test of dominant (p=.05) and non-dominant hand (p=.03)
Mapstone et al. 2013 USA	n=37 Mean age: 59y 81% male 0% AIDS 89% HAND CD4: 663 73% undetectable viral load 100% on cART	Cognitive battery: Reasoning speed, attention, concentration, executive, response inhibition and cognitive flexibility, language, memory, visuoperceptual and visuospatial organization	VO_{2peak}	Extent of cardiovascular fitness, as measured by VO_2peak	CD4 Nadir, number of years with HIV, Body mass index age	VO_2peak related to several cognitive domains (language, executive function, visual perception, visual and verbal memory) ($p<05$). Lower VO_2peak related with more severe HAND (OR=0.65,p=0.01)
Monroe et al. 2017 USA	n=263 with HIV Mean age: 50.5 100% male 10.3 % history of AIDS 93.5% on cART CD4=581 VL: 72% undetectable	Cognitive battery: Symbol Digit Modalities Test, Trail Making A& B	IPAQ Short Form	3 subgroups: low, moderate, and high PA levels based on IPAQ	HIV infection status, substance use, depressive symptoms, Hepatitis C infection, diabetes, hypertension, CD4 count, AIDS status, cART use, and detectable HIV RNA	High PA had protective effects on executive function (OR 0.34; learning (OR 0.27), memory (OR 0.28), motor function (OR 0.49), and global cognitive impairment (OR 0.32)
Ortega et al. 2015 USA	n=70 Mean age=43y 36% male % AIDS NR 96% on cART VL: 80% undetectable CD4: 601	Cognitive battery and brain volumes, Trail Making Tests A&B, Hopkins Verbal Learning Test-Revised, Digit-Symbol Modalities Test, letter fluency (FAS), verb fluency (VF) and Grooved Pegboard	Self-report of PA over past year	2 subgroups: physically active vs sedentary based on questionnaire	Recent and nadir CD4, viral load, duration of infection, cART use, body mass Index, age, sex, race, and education	Larger putamen volumes (p=.02) and better executive function (p=.04) but not motor performance in active group

PA: physical activity; OR: odds ratio; ALFs: active lifestyle factors; IPAQ: International Physical Activity Questionnaire; NCI: neurocognitive impairment; VO_{2peak}: peak oxygen consumption; HAND: HIV-associated neurocognitive disorders; IQ: intelligence quotient;. [a]For details on the cognitive tests used, refer to Heaton et al.[47]

Methodological Quality

Physiotherapy Evidence Database Reported Outcomes scores for the five randomized controlled trials were reported. Scores ranged from 3-8/10, with one study categorized as "good" quality,[469] three were "fair",[467,468,470] and one was "poor" quality[434] (Table 2).

Parameters of Exercise Interventions

Parameters of exercise interventions were identified by examining the protocols used in the interventional studies (Table 2). Four studies used a structured aerobic exercise intervention,[467,468,470,473] two investigated Tai Chi,[434,471] and two used a combination of aerobic and resistance exercise.[469,472]

Frequency of exercise interventions ranged from 1-3 times per week, and exercise session duration was typically 60 minutes. Program duration ranged from 8 weeks to twelve months. Mean total dose of exercise (i.e., hours/session * sessions/week * weeks of program) across seven of the interventional studies was 26.6 hours (range, 10-52). One study involved marathon training, therefore, the training dose varied throughout the intervention.[473]

Intensity of aerobic interventions was variably prescribed using 75-85% of age-adjusted maximal heart rate,[467] 60-80% of peak oxygen consumption[34] or maximal heart rate,[38] 60%-75% of maximal heart rate,[469] 40-75% of heart rate reserve,[470] and moderate to vigorous intensity indicated by Borg ratings of perceived exertion, respectively.[470,472] The resistance protocol in one study was 60%-80% of 1-repetition maximum.[469] In another study, training protocol was 70% of 1-repetition maximum for 1–3 sets of 8–15 repetitions.[472]

Assessment Tools for Cognition, Fitness and Physical Activity/Exercise

Five interventional studies[434,467–469,473] used the cognitive subscale of the Medical Outcomes Survey-HIV to evaluate self-reported cognition (Table 2). One study used the confusion-bewilderment subscale of the Profile of Mood States scale,[434] while two others used the Functional Assessment of HIV Infection,[471,472] and one study used the Montreal Cognitive Assessment, the Trails A, and the Trails B test.[470] All non-interventional studies employed neuropsychological batteries to assess cognitive domains typically affected by HIV infection[47] (Table 3). Cumulative scores were used to determine overall cognitive function.[475]

Physical fitness was assessed using peak oxygen consumption in two studies, which reported mean baseline values of 30.0[467] and 20.3 ml/kg/min.[156] Other studies used endurance tests to estimate fitness levels.[469,470,472] Six non-interventional studies used self-report questionnaires to estimate the extent of physical activity from the previous 72 hours,[150,154,155] previous week,[151,153] and past year.[152] In two studies, the International Physical Activity Questionnaire short form was used.[151,153] Participants in another study were simply asked two questions about their exercise habits "Do you participate in a regular program of exercise?” and "Were you exercising regularly before you learned about your HIV status?".[157]

Associations between Physical Activity/Exercise and Cognitive Function

All eight non-interventional studies showed positive relationships between physical fitness and various aspects of cognition in people living with HIV (Table 3). Fazeli et al.[150] reported that an active lifestyle was independently associated with better verbal, executive function, processing speed, recall, and working memory performance on the neuropsychological battery. Two studies conducted by Dufour et al.[154,155] showed that physical activity was associated with lower rates of impairment in working memory and speed of information processing. Fazeli et al[150] noted a positive association between an active lifestyle and higher verbal, executive function, speed of information processing, recall, and working memory performance. Another study found a negative relationship between moderate physical activity and neurocognitive impairment.[151] Mapstone et al.[156] noted positive associations between peak oxygen consumption and several cognitive domains (i.e., verbal and visual memory, perception, language). Monroe et al.[153] found that higher physical activity levels reduced the likelihood of impairment in executive function, learning, memory, motor function, and global cognition. Ortega et al.[152] showed that physically active people with HIV had better performance on executive function tests (but not motor function tests) and larger putamen volumes on magnetic resonance imaging than those who were physically inactive. In contrast, Honn, Para, Whitacre, and Bornstein[157] reported improvements in motor, but not executive function of the active participants.

Effectiveness of Exercise Interventions

Only one randomized controlled trial, which used a combination of aerobic and resistance exercise, demonstrated a beneficial effect of exercise on cognition compared to non-exercising control.[469] One single cohort study[471] also found a positive effect of Tai Chi on the cognitive subscale of the Functional Assessment of HIV Infection (Table 2). The other six interventional studies found no effect of exercise on cognitive function, whether it was self-reported,[434,467,468,472,473] or measured with cognitive testing.[470] No authors reported any adverse events associated with the interventions.

One interventional study included a qualitative assessment of cognitive outcomes,[434] the findings of which were elaborated on in a doctoral thesis.[474] Participants expressed sentiments such as, "Since I started, my attention span is better. I feel in control of my body and my mind. It is easier to do things every day…" and "Using my mind to be more precise as to the direction it takes the rest of my body".[474]

Discussion

The notion of using exercise as a therapeutic tool to improve cognition in the HIV population is relatively novel. To our knowledge, this study is the first to map the literature on physical activity and cognition in HIV. From the limited available literature, physical activity appears to be safe for people with HIV, as there were no adverse events reported in the 16 studies reviewed.

Exercise guidelines for people living with HIV were recently published by the American College of Sports Medicine,[476] and have since been adapted.[325] These guidelines are similar to those created in 1995, in which researchers recommended healthy adults participate in thirty minutes of physical activity on most, if not all, days of the week.[477] Although some of the studies were conducted before the guidelines were updated in 2014, they provide a standard reference point for comparison across studies.

The exercise parameters used in the interventional studies reviewed were not fully aligned with the guidelines.

Grace, Semple, and Combrink[325] provide exercise guidelines based on stage of infection (asymptomatic, symptomatic, or AIDS, as defined by the Centers for Disease Control[19]). They recommend aerobic exercise five times per week for asymptomatic participants, 3-5 times per week for symptomatic participants, and 3 days per week for those with AIDS.[325] The included studies did not consider stage of infection in the prescription of exercise frequency. Three sessions per week were implemented in four studies, two of which[467,468] involved asymptomatic people with HIV, while three studies scheduled two sessions per week,[434,469,472] and another study scheduled only one weekly session.[471] In contrast, session duration was within the range of 30-60 minutes recommended by the American College of Sports Medicine[476] in all but one interventional study.[467] Overall, the findings suggest that the weekly dose of exercise (duration * frequency) in the included studies was lower than that recommended by Grace, Semple, and Combrink.[325]

Similarly, stage of infection was not consistently factored into exercise intensity prescription. For example, in one study involving only people with AIDS, <60-70% of heart rate reserve was used (almost double that recommended by Grace, Semple, and Combrink).[434] However, in the two studies with asymptomatic participants, the intensities prescribed were consistent with the guidelines.[467,468] In other studies, participants' stages of infection varied or were not reported.[470,471,473]

Resistance training has also been recommended for people living with HIV - 3 days per week at 65-85% at 1-repetition maximum for asymptomatic individuals; 2-3 days per week at 55-85% of 1-repetition maximum for symptomatic individuals, and 2 days per week at 35-50% of 6-10-repetition maximum for those with AIDS.[325] Two interventional studies incorporated resistance exercise but did not indicate the stage of infection of the participants.[469,472]

The neuropsychological cognitive batteries used in the non-interventional studies have been touted as the “gold standard” for measuring cognition in HIV because they provide a comprehensive assessment.[46] However, they are also costly, time-consuming, and not widely available, even in high-income countries.[478] In contrast, the standardized patient-reported questionnaires used in the interventional studies require less time and include the end-user’s perspective. In people with HIV, the cognitive subscales of the Medical Outcomes Survey-HIV and Functional Assessment of HIV Infection are reliable (i.e., Cronbach’s alpha of .84),[479] whereas the cognitive domain of the Profile of Mood States scale has not been well studied in this population.[433]

In the two studies that measured physical fitness using peak oxygen consumption, the values reaffirmed previous reports of significantly reduced aerobic fitness in people with HIV.[156,467] While the self-reported questionnaires used in several studies to estimate physical activity are subject to recall bias, there is evidence that shorter recall periods can improve response accuracy.[480,481] Some self-report questionnaires did not provide information on the quantity, frequency, and nature (leisure versus work-based) of physical activity.[154,155] The International Physical Activity Questionnaire[368] was used in two non-interventional studies;[151,153] however, it has been shown to both under- and over-report the extent of physical activity.[370]

Encouraging evidence was found in the non-interventional studies regarding positive associations between physical fitness and cognition in people living with HIV. The finding of a significant relationship between physical activity and putamen volume[152] is consistent with a previous report of larger brain volumes in older women after six months of aerobic training.[482] As well, all investigators reported direct correlations between physical activity levels and multiple cognitive domains, in keeping with previous reports involving participants with neurological conditions[458,459,483] and the general population.[484] However, cognitive function can also predict one's participation in physical activity, suggesting that this relationship may be bidirectional.[485]

The dearth of positive outcomes of aerobic interventions on cognition reported in most of the interventional studies reviewed was surprising considering the mounting evidence in other populations. Recent systematic reviews have confirmed that exercise enhances cognitive function in the general population,[484,486] and there is encouraging evidence that this is the case in neurological conditions, such as stroke,[458] multiple sclerosis,[459] and Parkinson's disease.[459,483]

Methodological factors that could have contributed to the paucity of exercise-induced positive results include recall bias due to reliance on self-reported measures and lack of blinded assessors in all but one randomized controlled trial.[469] The prescribed dose of exercise was lower than the recommended exercise guidelines, and could have contributed to the null results. Characteristics of participants may also have influenced the direction of the findings. Older age, higher viral load, and lower T lymphocyte count are known risk factors for developing cognitive impairment in people living with HIV.[67,487,488] The mean age of participants in most of the included interventional studies (except for Brown, Claffey, and Harding[472]) was less than 50 years. Given that older people with HIV have a higher risk of developing cognitive impairment,[111,112,487] it may be less likely that cognition would be impacted by exercise in these younger cohorts. All participants in two interventional studies were asymptomatic,[467,468] thereby restricting the likelihood of significant cognitive concerns. Finally, most did not screen for, and more than half excluded those with severe cognitive impairment during screening,[434,469–471] which could limit the ability to identify cognitive benefits of exercise in these studies.

Additionally, the type of cognitive assessment could also have influenced the results of the interventional studies. Only one interventional study used objective measures of cognitive function (the Montreal Cognitive Assessment, Trails A & B) as their primary outcomes;[470] the rest of the studies used measures of self-reported cognitive function.[434,467–469,471–473] However, the Montreal Cognitive Assessment is not an acceptable screening tool, due to its poor sensitivity for detecting cognitive impairment in people living with HIV.[489,490] This study also had a sample size of only 11 participants.[470] Authors of many of the interventional studies did not report participants' viral load,[434,467,468,470–473] or both viral load and T lymphocyte count,[434,470–472] which precluded determination of HIV severity. Also, in three interventional studies, the majority of participants were on antiretroviral treatment,[434,469,473] whereas in another study, none of the participants were taking antiretrovirals,[467] and in the remaining four this information was not reported.[468,470–472]

A contributing factor to the positive results in one of two trials may have been the use of a longer exercise program (6 months) and higher overall dose of exercise (52 hours) compared to most other studies.[469] In a previous trial involving women with cognitive deficits, benefits to cognition with resistance training were observed only after 6 months.[491] Nevertheless, treatment exposure cannot explain the results of the second positive trial in our review because the overall dose of the exercise intervention was the lowest of all studies reviewed (10 hours),[471] and no cognitive improvements were seen in the marathon-training intervention where participants exercised for twelve months.[473]

Indeed, in the general literature the effect of dose of aerobic exercise on cognition remains unclear;[492] however, mounting evidence suggests that there may be a dose-response effect of total exercise duration per week on cognition.[492] Importantly, it also appears that one's fitness response to aerobic exercise is a more potent predictor of cognitive function than exercise dose.[492] Investigators have hypothesized that more vigorous forms of exercise may confer greater benefits to cognitive health, since aerobic fitness gains are directly related to exercise frequency and intensity.[493] There are currently no exercise guidelines for improving cognitive function; however, it does appear that interventions that comply with current aerobic exercise guidelines for healthy individuals are effective in other clinical populations.[493] Therefore, we recommend that aerobic interventions aimed at improving cognitive function also aim to improve cardiovascular fitness.

Study Strengths and Limitations

To ensure rigor of our scoping review, we followed the framework developed by Arksey and O'Malley,[461] supplemented by Levac et al.[460] We consulted with people with HIV and health care providers to assist in shaping our research question. Also, to limit bias when searching for studies for inclusion, we did not include outcomes related to cognitive function in the search strategy; rather, we screened abstracts to find outcomes related to cognition. This strategy proved to be effective, as we found many articles for inclusion where the main outcomes were related to quality of life, but used cognitive function as a secondary outcome. We also used two independent reviewers of the abstracts, and a third reviewer to resolve any disagreements to further reduce any bias associated with the screening process.

Study limitations include restricting our searches to five databases without searching the grey literature, which could have limited the breadth of this topic. We also stipulated that only studies published within the past 20 years would be included in the review, our rationale being that the advent of combination antiretroviral therapy might confound comparability of studies published before and after this important milestone. Finally, all included studies were conducted in developed countries, thus limiting the external validity of the findings.

Conclusion

The extent of positive associations between physical activity and cognition reported in the non-interventional studies included this scoping review suggest that physical activity may play a role in preserving or improving cognition in people living with HIV. However, the limited interventional studies to date have yielded little empirical evidence to support this supposition.

Future Directions

Future randomized controlled trials should comply with current exercise recommendations by considering the stage of infection for exercise prescription.[325] Finally, investigations into the role of exercise to enhance cognition in people with HIV should identify subgroups within the HIV population who will benefit the most and specify parameters of exercise that will optimize outcomes.

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Chapter 6-Effects of Exercise on Cognitive Performance in Older Adults: A Narrative Review of the Evidence, Possible Mechanisms, and Recommendations for Exercise Prescription

This chapter is a manuscript that was submitted to *Ageing International* in February 2019 where we outline the literature evaluating exercise interventions among older HIV-negative individuals without cognitive impairment, as well as important underlying mechanisms. We also make recommendations regarding exercise prescription. While there is less literature evaluating the impact of exercise interventions among individuals with cognitive impairment, it is likely that similar mechanisms are taking place, and there is emerging evidence that even individuals with severe cognitive impairment (ie. dementia) can benefit from exercise training. Growth hormones such as brain derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) have not been studied among PLWH, with the exception of Dudgeon et al. (2012) who found no significant change in IGF levels among PLWH following their exercise intervention.[494] Since only one study was cited that evaluated the impact of exercise on growth factors among PLWH, we will discuss research conducted with HIV-negative individuals in this chapter. Regarding our statements in Chapter 5, which suggested that increased fitness may be necessary to induce cognitive improvements, emerging evidence contradicts that notion. We discuss this controversy in detail in this chapter.

Copyright Statement

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Contribution Statement

I developed and wrote the manuscript with assistance from Dr. Marilyn MacKay-Lyons and Dr. Gail Eskes.

Abstract

Physical activity and exercise have emerged as potential methods to improve brain health among older adults. However, there are currently no physical activity guidelines aimed at improving cognitive function, and the mechanisms underlying these cognitive benefits are poorly understood. The purpose of this narrative review is to present current evidence regarding the effects of physical activity and exercise on cognition in older adults, identify potential mechanisms underlying these effects, and make recommendations for exercise prescription to enhance cognitive performance. The review begins with a summary of evidence of the effect of chronic physical activity and exercise on cognition. Attention then turns to four main mechanisms that appear to underlie exercise-induced cognitive improvement, including the upregulation of growth factors and neuroplasticity, inhibition of inflammatory biomarker production, improved vascular function, and hypothalamic-pituitary-adrenal axis regulation. The last section provides an overview of exercise parameters known to optimize cognition in older adults, such as exercise type, frequency, intensity, session duration, and exercise program duration.

Keywords: physical activity; exercise; cognition; successful aging; older adults

Background

In 2017, the number of people aged 60 years or over was 962 million worldwide; this figure is expected to reach nearly 2.1 billion by the year 2050.[495] This demographic shift toward an older population increases the prevalence and severity of chronic diseases.[496] Dementia is characterized by difficulties with memory, language, thinking, and activities of daily living[497] and can be due to a variety of etiologies, including Alzheimer's pathology and vascular disease.[498] Currently, 35.6 million people worldwide are living with dementia;[499] by the year 2030, that number is expected to double to 75.6 million, making it a major public health priority.[500] Mild cognitive impairment (MCI), is an intermediate stage in the continuum from normal cognition to dementia; it is estimated that 60–65% of people with MCI will develop clinical dementia during their lifetime.[501] Slowing or halting this progression can have implications for quality of life and health care savings. Indeed, if the progression to Alzheimer's disease (the commonest form of dementia) could be delayed by one year, total costs could be reduced by an estimated 113 billion American dollars by the year 2030.[502]

Physical activity and exercise have emerged as potential methods to improve brain health among older adults. However, there are currently no physical activity guidelines aimed at improving cognitive function, and the mechanisms underlying these cognitive benefits are poorly understood. Thus, the main purpose of this narrative review is to present current evidence regarding the effects of chronic physical activity and exercise on cognition, identify potential mechanisms underlying these effects, and make recommendations for exercise prescription to enhance cognitive performance. Our focus is mainly on healthy older adults over 50 years of age. The review begins with a summary of evidence regarding the association between exercise and cognition, adding to older literature reviews such as those by Kirk-Sanchez & McGough (2014) and Bherer, Erickson, & Liu-Ambrose (2013).[503,504] Attention then turns to four main mechanisms that appear to underlie exercise-induced cognitive improvement among older adults – (i) upregulation of growth factors and neuroplasticity, (ii) inhibition of inflammatory biomarker production, (iii) improved vascular function, and (iv) hypothalamic-pituitary-adrenal (HPA) axis regulation. The last section provides an overview of exercise parameters thought to optimize cognition in older adults.

Physical Activity and Cognitive Function

Evidence from prospective and cross-sectional studies suggest that physically active persons have a significantly reduced risk of cognitive impairment and dementia. Hamer and Chida (2009)[455] conducted a meta-analysis on physical activity and risk of neurodegenerative disease that involved 16 prospective studies of 163,797 participants without dementia. Among participants who were physically active, there was a 28% reduction in risk of dementia and a 45% reduction in Alzheimer's disease.[455] A later meta-analytic review of 21 longitudinal studies of 89,205 adults over the age of 40 also found that higher levels of physical activity was associated with reduced risk of cognitive decline and dementia.[505] Another meta-analysis of 15 prospective studies found that physically active individuals (mostly older adults) reduced their risk of cognitive decline by 38%.[506] Meta-analyses by Daviglus et al. (2011) and Beckett, Ardern, & Rotondi (2015) each with 9 prospective studies among older adults, determined that physically active older adults reduced their risk of developing Alzheimer's disease, relative to their inactive counterparts.[507,508] The evidence from prospective and cross-sectional research indicates that a physically active lifestyle is associated with a reduction in risk of cognitive impairment later in life.

Exercise and Cognitive Function Among Older Adults: Meta-analytic Evidence

There is evidence emerging from randomized controlled trials (RCTs) and meta-analyses to suggest that exercise interventions can improve cognition among older adults. The most common experimental intervention in the meta-analyses evaluating the impact of exercise on cognition is aerobic exercise (AE), followed by resistance exercise (RE), a combination of AE and RE, and mind-body exercise (Tai Chi, Qigong, dance, or yoga). The meta-analyses are summarized in Table 1 and are discussed below.

Table 1: Meta-analyses of RCTs evaluating the impact of exercise interventions on cognition

First author, year	# of included studies # of participants	Population(s)	Other selection criteria	Experimental exercise (# of studies)	Exercise dose	Control treatment	Meta-analysis results
Barha (2017)	39 RCTs (5,256 participants)	Healthy older adults 45+ years	• Mind-body exercise trials excluded • Studies evaluating global cognition only excluded	AE(n=19) RE (n=9) Combined AE + RE (n=13)	Frequency: 1-5 sessions/week Intensity: variable Duration:8-52 weeks	Active and inactive controls	• AE improved executive functioning relative to controls (g = 2.064) • AE interventions benefitted global cognitive function and executive functions more than RE • Combined training benefitted global cognitive function and episodic memory more than AE and RE
Colcombe (2003)	18 RCTs 197 participants	Older adults 55-80 years	• Date range 1966-2001 • Measure of aerobic fitness	AE (49% of participants) or combined AE + RE (51% of participants)	Frequency: NR Intensity: NR Duration: 1-3 months (38%), 4-6 months (36%) 6+ months: (26.7%)	NR	• Exercise had the greatest effect on executive function (g=0.68) • Combined training produced larger improvements in cognition than AE alone (g=.59 vs. 0.41) • Long term training associated with largest improvements in cognition (g=0.674)
Etnier (1997)	134 studies (17 clinical trials) 420 participants	All ages (exact ages NR)	• NR	AE and RE (numbers NR)	NR	NR	• Moderate effect of chronic exercise on cognition (g=.33) • Effect of clinical trials on cognition (g=.18) • Exercise session duration, frequency, and program duration were not significant moderators of cognition
Gothe (2015)	22 (15 RCTs) 2,012 participants	All ages (mean age 62 years)	• Objective measure of cognitive function	Hatha yoga (n=8) Iyengar yoga (n=3) Integrated yoga therapy (n=1) Sahaj yoga (n=1)	Frequency: 1-5 sessions/wk, Session duration: 45-120 mins Duration:1-6 months	Active and inactive	• Yoga had a moderate effect (g= 0.33) on cognition • Largest effect on attention and processing speed (g=0.29) followed by executive function (g=0.27) and memory (g=0.18)
Kelly (2014)	25 RCTs 2,217 participants	Healthy older adults with no cognitive impairment 50+ years	• Cardiovascular disease, other medical, psychiatric, or neurological conditions were excluded • Date range 2002-2012	AE (n=19), RE (n=7), Tai Chi (n=3)	Frequency: 1-3 sessions/wk Intensity: variable Total duration: single bout to 1 year	No exercise, non-aerobic exercise, education, social or mental activities	• No improvements in AE vs stretching/toning on cognition • Significant improvements for RE vs. stretching/toning in reasoning (p<0.005) and Tai Chi vs no exercise in attention (p<.001) and processing speed(p<.00001).
Northey (2018)	36 RCTs 2,748 participants	Older adults with and without cognitive impairment 50+ years	• Neurological and mental health populations excluded • Unsupervised exercise interventions excluded • Interventions <4 weeks excluded	AE (n=18), RE (n=13, multicomponent (n=10), tai chi (n=4), yoga (n=2)	Frequency: 1-5 sessions/wk Session duration: 20-90 min Intensity: variable, many NR Total duration: 6-52 weeks	Active (stretching, balance and tone, sham cognitive training, health education) and inactive (social interaction), no-contact	• Improved cognitive function (SMD=0.29; p<0.01) with exercise of all types • AE, RE, combined, and Tai Chi interventions had significant effect estimates (p<.01) • Session duration >45 min ≤60 min associated with improved cognition (p<0.01) • Moderate (p=0.02) and vigorous (p<0.01) intensity exercise (not low-intensity) associated with improved cognition
Sanders (2019)	36 RCTs 2,007 participants	Older adults with and without cognitive impairment 50+ years	• Treatment duration >4 weeks • Excluded if did not specify exercise intensity • Excluded studies if dose parameters were gradually increased	AE (n=21) RE (n=18) Multicomponent (n=10) Balance (n=2)	Frequency: 1-5 sessions/wk (mean=2.62) Session duration: 20-60 mins/session (mean=50.1 mins) Program duration: 4-52 weeks (mean=22.3 weeks) Mean total dose: 2720 mins	Active and passive controls	• Small positive effect of exercise on executive function (d= 0.27) and memory (d= 0.24) in healthy older adults • Exercise dose (type, session, duration, program duration, frequency, intensity) did not predict changes in cognition • Shorter exercise sessions and higher frequency sessions predicted larger effects in those with cognitive impairment
Scherder (2014)	8 RCTs 642 participants	Sedentary healthy older adults 55+ years and older adults with cognitive impairment	• Published in English	AE (n=8)	Frequency:1-7 sessions/wk Session duration: 30-60 mins Program duration: 4 weeks-1 year	Active and passive controls	• Walking improved set-shifting and inhibition in sedentary older adults without cognitive impairment (d=0.36) • No effect of walking on executive function among older adults with cognitive impairment (d=0.14)

First author, year	# of included studies # of participants	Population(s)	Other selection criteria	Experimental exercise (# of studies)	Exercise dose	Control treatment	Meta-analysis results
Smith (2010)	29 RCTs 2,049 participants	Healthy adults and MCI Mean age 18+ years 23 RCTs with older adults	• Treatment duration: >1 month	Supervised AE (n=29)	Frequency: 1-5 sessions/wk Intensity: variable, many NR Duration: 8-72 weeks	Non-aerobic exercise, wait-list, education, stretching, social activities	• Modest improvements in attention and processing speed (g=0.158), executive function (g=0.123) • Exercise intensity and duration did not moderate effects on memory • Older adults demonstrated larger improvements in working memory compared to younger participants
Wayne (2014)	11 RCTs 2,553 participants	Older adults with and without cognitive impairment mean age 60 years, except 1 study with adults	• Measure of cognitive function	Tai Chi (n=11)	Frequency: 1-4 sessions/week Intensity: variable, many NR Duration: 10 weeks-1 year	Active and non-active controls	• Large effect of Tai Chi vs no exercise on executive function (g=0.90) and moderate effect vs exercise controls (g=0.51) in healthy older adults
Wu (2018)	32 RCTs 3,624 participants	Older adults with and without cognitive impairment aged 55-80 years	• Measure of cognitive function	Tai-Chi (n=18) Yoga (n=8) Dance (n=6)	Frequency: 1-4 sessions/week Intensity: NR Session duration: 20-60 mins/ session Duration: 2-48wks	Active and non-active controls	• Improvements in global cognition compared with controls (mean difference=0.92), particularly cognitive flexibility, working memory, verbal fluency, and learning • Moderate dose (60-120 mins per week) significantly improved global cognition compared to controls
Young (2015)	12 RCTs 754 participants	Healthy older adults >55 years	• Measure of CV fitness	AE (n=12)	Frequency: 1-5 sessions per week Intensity: variable Duration: 8-26 weeks	No treatment, non-aerobic exercise, social or mental activities	• No benefit of AE vs active or inactive controls on any of the 11 cognitive domains • Increased fitness did not coincide with improvements in cognition
Zhang (2018)	19 RCTs 2,539 participants	60+ years with and without cognitive impairment	• Measure of cognitive function • Articles in English or Chinese	Tai Chi (n=12) Yoga (n=4) Qigong (n=2) Pilates (n=1)	Frequency: 1-7 sessions/wk Session duration: 20-120 min Intensity: NR Duration: 8-52 weeks.	Active or passive controls	• Benefits global cognition (g=0.23), executive functions (g =0.25-0.65), learning and memory (g=0.37-0.49), and language (g=0.35). • Mind-body exercise more effective for older adults without cognitive impairment • Total training time predictor of global cognition, executive function, and language

Notes: RCT, randomized controlled trial; MCI, mild cognitive impairment; NR, not reported; min, minutes; AE, aerobic exercise; RE, resistance exercise

Meta-analytic evidence supports the positive effects of AE and RE on cognition among older adults. Colcombe & Kramer (2003) determined that there were positive effects of AE and combined (AE and RE) training on cognition in their meta-analysis of 18 RCTs in sedentary older adults.[509] Scherder et al. (2014) revealed in their meta-analysis of 8 RCTs that walking improved set-shifting and inhibition in sedentary older adults without cognitive impairment.[510] Northey, Cherbuin, Pumpa, Smee, and Rattray (2018) conducted a meta-analysis of 36 RCTs among older adults and determined that AE, RE, and combined (AE and RE) interventions are all effective in improving cognition in older adults.[511] The most comprehensive meta-analysis to date evaluating cognitive outcomes following exercise interventions revealed a strong effect of AE on executive function among healthy older adults.[512] However, it is important to note that this meta-analysis had a large proportion of female participants and it is thought that exercise may elicit larger improvements in cognition in women than in men.[509,513]

There is also evidence that mind-body exercise can have a positive effect on cognition among older adults. Wu et al. (2018)[514] discovered significant improvements in global cognition, cognitive flexibility, working memory, verbal fluency, and learning in their meta-analysis of 32 RCTs among older adults with and without cognitive impairment. Zhang, Li, Zou, Liu, and Song (2018)[515] revealed in their meta-analysis of 11 RCTs that mind-body exercise had a significant effect on global cognition, executive function, learning, memory, and language among older adults with and without cognitive impairment. The authors determined that cognitively intact older adults benefitted more from mind-body exercise than those with existing cognitive impairment.[515] Similarly, a 2014 meta-analysis of 11 RCTs by Wayne et al. (2014)[516] revealed a robust effect of Tai Chi on executive function in older adults without cognitive impairment. Finally, Gothe and Mcauley (2015)[517] revealed a moderate effect of yoga compared to controls on measures of attention, processing speed, memory, and executive function in their meta-analysis of 15 RCTs. It is important to note, however, that this meta-analysis was conducted with participants of all ages, and only 6 of the included RCTs were conducted with older adults.[517]

In contrast with the those findings, Sanders and colleagues (2019)[518] conducted a large meta-analysis of 36 RCTs and revealed only a small effect of AE, RE, combined AE and RE, and balance exercise on executive function and memory among healthy older adults. These results may be explained by the exclusion of studies that did not specify exercise intensity and interventions whose dose parameters were gradually increased (which is recommended by the American College of Sports Medicine guidelines for exercise prescription[519]). Other meta-analyses have also found conflicting evidence on this topic. A Cochrane meta-analytic review by Young et al. (2015)[520] of 12 RCTs concluded that there is little evidence that AE of varying doses (for example, three interventions lasted eight weeks and one offered a single exercise class per week) improves cognition in healthy older people. While this meta-analysis was focused on older adults, the most recent included study was from 2012, and more compelling evidence on this topic has been published since then.[511,512] A 2014 meta-analysis of 25 RCTs on cognition in healthy older adults by Kelly et al. (2014)[456] demonstrated beneficial effects of RE versus stretching on reasoning performance, and Tai Chi on attention and processing speed compared to no exercise, but no effect of AE on cognition in healthy older adults. These findings can be explained by the fact that the authors only included studies conducted between 2002-2012, thereby limiting the studies for inclusion.[456] Furthermore, they did not exclude acute or short-term studies, which may have influenced their results.[456]

Further conflicting evidence comes from a meta-analysis by Etnier and colleagues (1997)[521] who determined that AE and RE have a small overall effect on cognitive performance. However, this study does not adequately report their study selection criteria and exercise dose.[521] Despite this, their analysis of 134 studies revealed that the largest effect sizes were found among adults aged 45-60 years regarding exercise and cognitive performance.[521] Smith et al. (2010) published a meta-analysis of the effects of AE on cognitive performance consisting of 29 RCTs that included adults with and without cognitive impairment.[484] Their results revealed modest improvements in attention, processing speed, executive function, and memory in participants randomly assigned to an AE intervention compared to non-aerobic exercising controls.[484] It is worth noting, however, that they also used an inclusion criterion of mean age of 18 years older for their review.[484] Although the majority of the studies they included in the meta-analysis report on older adults, seven of the included studies have substantially younger age ranges, which may not generalize well to older adults.[484]

Despite these conflicting reports, 12 of the 13 meta-analyses we have reviewed have found a beneficial effect of exercise on at least one aspect of cognition, albeit some studies have determined only a modest effect. Taken together, this evidence suggests that exercise may have beneficial effects on cognition among older adults. In the RCT exercise literature, there is a lack of standardized reporting of exercise interventions (i.e., frequency, intensity, time, and type), which makes it challenging to determine what constitutes an effective intervention. Future research should address methodological concerns and investigate the optimal exercise dose for improving cognition among older adults. The next section of this review addresses potential mechanisms that may explain exercise-induced improvements in cognition. See figure 1-Overview of potential mechanisms underlying cognitive gains with physical activity and exercise.

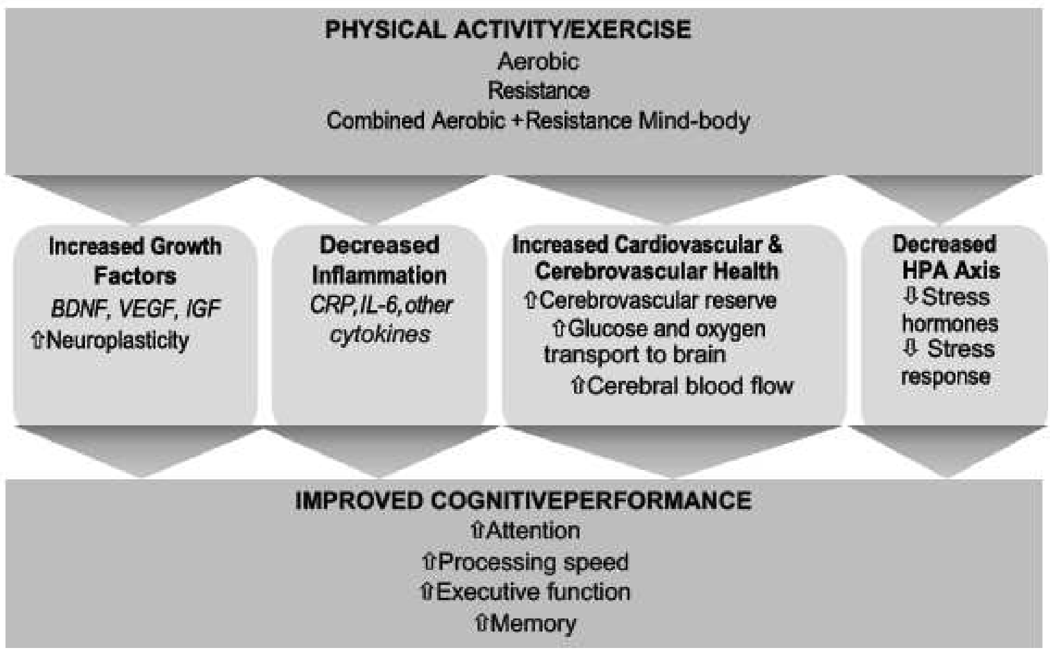

Figure 1: Overview of potential mechanisms underlying cognitive gains with physical activity and exercise

Exercise, Neuroplasticity, and Growth Factors

With age, the gray and white matter regions of the human brain begin to atrophy, particularly in the prefrontal cortex and the hippocampus.[522] According to a 2-year longitudinal study using magnetic resonance imaging, older adults without dementia can expect to have 1-2% of hippocampal atrophy per year, while individuals with Alzheimer's disease experience larger volume loss.[523] Other studies have shown that increasing age is associated with lower serum[524,525] and plasma[526] levels of brain-derived neurotrophic factor (BDNF), a key growth factor in the exercise-brain health interaction, as measured by enzyme-linked immunosorbent assays.

Neuroplasticity, the brain's ability to create and reorganize synaptic connections, appears to be an important mechanism for improved cognition with exercise among adults of all ages. An RCT conducted by Colcombe et al. (2004)[527] using functional magnetic resonance imaging revealed aerobically trained older adults demonstrated increased neural activity in the frontal and parietal regions of the brain compared to controls. Similarly, Voss et al.'s (2010)[528] RCT revealed improvements in functional connectivity in regions that support the default-mode and frontal executive networks following 12 months of AE training in older adults. A cross-sectional study of 165 healthy older adults found that individuals with higher fitness levels had preserved hippocampal volumes and better performance on a spatial memory task compared to those with low fitness levels.[529] It appears evident that neuroplasticity is underlying some of the improvements in cognition with physical activity. Our focus turns to the role growth factors such as BDNF, insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) play in exercise-induced improvements in cognitive performance among older adults.

High-level evidence indicates that there is a link between exercise interventions and upregulation of growth factors in older adults. A meta-analysis by Dinoff et al. (2016) of 29 studies involving AE and RE in 910 healthy adults of all ages revealed an overall increase in BDNF levels following exercise interventions.[530] The authors determined that gender and mean age were not correlated with changes in BDNF levels, indicating that BDNF increases with exercise regardless of age or gender.[530] It is important to note that the authors identified significant heterogeneity of the included studies regarding study populations, exercise interventions, measurement methods, and study quality but this is the highest-quality evidence available on this topic to date.[530] In contrast, a meta-analysis revealed that AE and combined (AE and RE) training did not significantly increase BDNF levels compared to controls; however, this analysis only included 3 RCTs (all with older adult participants).[512]

There is some evidence that exercise type affects upregulation of specific growth factors. Dinoff et al.'s (2016) meta-analysis of AE and RE interventions in healthy adults concluded that AE, but not RE, had a significant effect on peripheral BDNF levels.[530] As well, an RCT of 66 older adults with MCI revealed that an acute bout of AE significantly increased serum BDNF and IGF-1 levels, whereas an acute bout of RE increased only serum IGF levels.[531] Cassilhas et al. (2007) conducted an RCT with 62 older adult male participants with two experimental groups (24 weeks of high-intensity RE and moderate-intensity RE), revealing significant improvements in serum IGF-1 levels in both experimental groups compared to controls. From the available literature, it appears as though AE interventions tend to increase BDNF levels, while RE interventions increase IGF-1 levels.

While some growth factors appear to increase with exercise, less is known about how this association impacts cognitive performance. A 2014 RCT of 49 older sedentary women revealed that a 16-week program of twice-weekly aerobic, resistance, and motor exercises elevated serum BDNF levels and improved verbal fluency, processing speed, attention, and mental switching performance in exercisers compared to waitlist controls.[533] Importantly, larger effect sizes were found in this study regarding cognitive performance than in similar studies involving single or bimodal forms of exercise.[533] Another RCT involving a 1-year moderate-intensity AE intervention with 90 older adults determined that that a positive relationship existed between age and serum BDNF levels in the AE group, whereby adults over the age of 65 experienced the largest increases in BDNF following the intervention.[525] Importantly, they revealed that increases in serum BDNF and improved executive function in the AE group varied by age, with the oldest individuals reaping the largest benefits to cognitive performance.[525] Despite the findings from Dinoff et al. (2016) identifying no association between age and BDNF upregulation, these findings indicate that older adults may experience larger improvements in cognition than younger individuals. Regarding IGF-1 levels, an RCT of 62 older adults revealed significant improvements in both cognitive performance and serum IGF-1 levels following an RE intervention.[532] Stein et al. (2018) performed a systematic review of seven randomized studies evaluating the effect of exercise interventions (4 AE, 2 RE, 1 combined AE and RE) on IGF-1 levels and cognitive performance among older adults, revealing that three of the included studies augmented IGF-1 levels, three remained stable, and one reduced IGF-1 levels with beneficial effects on cognitive performance demonstrated in five of the included studies.[534] These results are explained by the aforementioned hypothesis that IGF-1 levels increase with resistance training; indeed, IGF-1 levels and cognitive performance improved in both RE interventions.[532,535]

Other RCTs have found contrasting results regarding growth factors and exercise. A study with 40 older adults assigned to an AE intervention or control group revealed that serum BDNF, IGF-I, VEGF levels were not significantly upregulated with exercise and there were no between-group differences in immediate or delayed recall, but IGF-I levels were related to hippocampal volume changes, and changes in IGF-I were associated with delayed recall performance.[536] An RCT of 33 older adults with MCI revealed that female participants improved on multiple tests of executive function despite a *reduction* in plasma BDNF levels following a 6-month high-intensity AE intervention while male participants increased plasma IGF-1 levels and improved their performance on an executive function task.[513] A similarly designed RCT by the same authors with glucose-intolerant older adults revealed improvements in executive function, reductions in plasma BDNF levels, and no change in plasma IGF levels.[537] Another RCT comparing 1 year of walking to stretching in healthy elderly participants did not find between-group differences in changes in serum levels of BDNF, IGF-I or VEGF; however, changes in growth factors of the walking group correlated with improved functional connectivity between the para-hippocampal and middle temporal gyrus using functional magnetic resonance imaging.[538] Finally, Erickson and colleagues did not find between-group effects of AE on serum BDNF levels, but they did find that hippocampal volume (which was increased in the AE group compared to controls) was associated with higher BDNF levels.[539]

Clearly, there are significant discrepancies regarding growth factors as a putative mechanism for improving cognitive performance in older adults. There are known problems with the measurement of growth factors in humans, which could help to explain these contrasting results. For example, Knaepen, Goekint, Heyman,

& Meeusen (2010) identified significant blood sampling and biochemical analysis concerns regarding measurement of BDNF levels, including clotting time, temperature storage, and a lack of corrected BDNF levels for the shift in plasma volume with exercise.[540] Similar issues have been identified with the measurement of IGF-1 levels.[534] Furthermore, peripheral BDNF levels are prone to significant diurnal fluctuations due to circadian rhythms.[541,542] For example, Maass et al. (2016) measured serum and plasma BDNF levels eight times during their study and found considerable fluctuations among their participants.[536]

Standardized protocols should be implemented and reported by researchers to reduce measurement error. It is also difficult to determine the extent to which peripheral BDNF levels correlate with central BDNF levels; only one study has found a positive association between peripheral and central BDNF levels, and that study was conducted with people with psychosis.[543]

Although there is a considerable discrepancy in the literature, it appears that BDNF levels are increased following AE interventions in people of all ages. Less is known regarding the upregulation of growth factors as a putative mechanism for improved cognitive performance in older adults. High-quality RCTs and meta-analyses that address measurement issues are needed to determine both the effect of exercise on growth factors and the relationship between exercise-induced increases in growth factors and cognitive performance in older adults.

Inflammation, Exercise, and Cognition

In aging adults, microglia and cytokines stimulate the production of pro-inflammatory markers, which promote changes in blood vessel permeability, endothelial cell function, and microvascular structure,[218] resulting in damage to neurons.[544] Acute and chronic inflammation can facilitate the release of reactive oxygen species and other neurotoxic factors.[545] The aging human hippocampus and basal ganglia have more enzymes involved in inflammatory processes than other brain regions; as such, they tend to be at higher risk of inflammatory damage.[546]

As people age, pro-inflammatory markers such as CRP (C-reactive protein), Interleukin (IL)-6 and -1 beta, and tumor necrosis factor alpha (TNF-alpha) increase[218] and are related to cognitive decline.[547] Systemic inflammation is present in chronic conditions such as type 2 diabetes, atherosclerosis[548] multiple sclerosis, and dementia.[549] Studies of older adults and individuals with type 2 diabetes revealed that those with higher levels of inflammation had smaller hippocampi and medial temporal lobes compared to those with low levels of inflammation.[550,551] A cross-sectional study of 3,298 multiethnic older adults reported that serum levels of IL-6 were negatively associated with Mini-Mental State Examination scores after adjusting for age, education, and vascular risk factors, leading the authors to conclude that elevated inflammation may have a direct impact on cognition.[552] A longitudinal study of 3,031 healthy older adults found that those with the highest concentrations of IL-6 and CRP had a 24% increased risk of developing cognitive impairment compared to individuals with low inflammation.[547]

There is encouraging evidence from a recent systematic review of 13 RCTs that healthy sedentary adults of all ages who participate in AE and RE can reduce inflammatory biomarkers.[553] Stronger effects were found in older adults, with high-intensity AE being the most effective in reducing inflammation.[553] A non-randomized study involving adults over 60 who participated in 16 weeks of aerobic, resistance, and neuromotor exercise demonstrated greater reductions in TNF and IL-6 and increases in peripheral BDNF in the exercise group than in the non-exercising group.[554] Further analyses revealed that exercisers with MCI had significant improvements in executive function and attention.[554] It is thought that AE may release muscle-derived anti-inflammatory substances, thereby reducing the function of pro-inflammatory cytokines in older human adults.[555]

Some promising evidence has emerged indicating that aerobic exercise in particular can reduce inflammatory markers in older adults. While there is evidence that inflammation can have a direct impact on cognition, little is known regarding the mediating role of exercise-induced changes in inflammation on cognitive performance in older adults. Future studies could further investigate the mechanisms underlying the effect of exercise on inflammatory markers and cognition.

Vascular Health, Exercise, and Cognition

Cardiovascular and cerebrovascular disease risk factors such as hypertension, dyslipidemia, diabetes, and hyperinsulinemia increase the risk of cognitive impairment and dementia.[556,557] An observational study followed 3,381 adults for 25 years and found that elevated blood pressure and higher fasting blood glucose increased the risk of cognitive impairment and dementia later in life.[557] Consistent with these results, a negative relationship between hypertension and attention, visuospatial, perceptual, memory, learning, psychomotor, and executive performance has been reported in older adults.[556] In the hypertensive brain, decreased vascular blood flow and metabolism in the putamen, globus pallidus, and left hippocampus contribute to higher rates of cognitive impairment in elderly individuals.[558,559] In older adults, reduced cerebral perfusion related to cardiovascular disease and aging may affect subcortical white matter pathways,[560] thereby reducing processing speed and accuracy. Blood vessel stiffening and fibrosis can be contributing factors,[561] and free radical production increases with age and cardiovascular disease, all of which can disrupt smooth muscle vasodilatory mechanisms.[562] Age and coronary heart disease also decrease cerebrovascular reactivity to carbon dioxide, thereby increasing the risk of neurological damage.[563]

The positive effects of AE on cardiovascular[564–566] and cerebrovascular[567,568] health among adults of all ages have been well established in the literature. Compared with age-matched sedentary controls, aerobically fit older adults have better cardiac function, including elevated stroke volume, wall thickness, and end diastolic volume.[569–571] Further, chronic AE in older adults results in improved cardiac output, ejection fraction, and left ventricular contractility.[570,572] A cross-sectional study of 307 participants revealed that healthy men aged 18-79 with better aerobic fitness had 17% higher cerebral blood flow compared to their sedentary counterparts.[567]

There may also be a link between improved cardiovascular and cerebrovascular function and cognitive performance. Vidoni et al. (2015) determined that changes in fitness levels mediated cognitive improvements in older adults who participated in an AE intervention.[492] Brown et al. (2010)[433] found a significant association between physical fitness, cerebrovascular regulation, and cognitive function in a cross-sectional study of 42 healthy older women. An RCT of older adults revealed that 12 weeks of AE training resulted in higher resting cerebral blood flow in the anterior cingulate region and improved immediate and delayed memory scores compared to controls.[573] Finally, higher fitness levels among female participants of all ages was associated with improved executive function and increased cerebral oxygenation in the frontal areas of the brain compared to women with low fitness levels.[574] Enhanced ability of cerebral blood vessels to respond to chemical, mechanical, or neural demands may be an important mechanism underlying exercise-induced cognitive improvements. Increased blood flow may increase endothelial nitrous oxide synthase expression, which promotes blood vessel vasodilation.[575] Exercise training is also known to enhance oxygen and glucose transport to the brain, thereby increasing cognitive efficiency.[576]

Despite the evidence that improved cardiovascular fitness is associated with improved cognition, two meta-analytic reviews have failed to support cardiovascular fitness as a moderator of exercise-induced cognitive gains in older adults.[509,520] Further evidence to refute the cardiovascular fitness hypothesis is provided by Smiley-Oyen and colleagues, who performed a mediational analysis within their RCT of 57 older adults and revealed improvements in executive function for those who performed AE; however, changes in aerobic fitness were unrelated to changes in executive function.[577] Finally, two other RCTs have found improvements in cognitive performance with RE, AE, and neuromotor exercise, independent of increases in cardiovascular fitness among older adults.[578,579]

There is no question that exercise has beneficial effects on cardiovascular and cerebrovascular function among older adults. Although the cardiovascular hypothesis for exercise-induced changes in cognitive performance in older adults is intuitive, the evidence from meta-analyses and RCTs indicate that this hypothesis alone is unable to explain improvements in cognition with exercise. Is it possible, however, that older adults can experience cardiovascular and cerebrovascular benefits with exercise without changes in aerobic fitness. Future research should further elucidate these relationships in order to develop recommendations regarding exercise dose.

Hypothalamic-Pituitary-Adrenal Axis, Exercise and Cognition

Another mechanism by which exercise could improve cognitive function is via the HPA axis. As individuals age, their ability to adapt and cope with stress diminishes.[580] Chronic stress can over-activate the HPA axis, which has important implications for glucose tolerance, neuroendocrine, and autonomic functions.[581] Acute stress has known detrimental effects on working memory, interference control, and cognitive flexibility, as evidenced by a recent meta-analysis of 51 experimental studies involving 2,486 adults of all ages.[582] However, the authors found that stress levels did not moderate the effect of cortisol on inhibition and working memory, and studies that utilized cortisol administration did not find an effect on executive functions overall.[582] The authors found that participant age did not moderate stress effects on executive functions, however, only three of their included studies were among older adults, therefore it is unlikely that these results can be applied to older adults. Indeed, there is longitudinal and cross-sectional evidence indicating that older adults with higher rates of chronic stress are 2.7 times more likely to develop Alzheimer's Disease,[583] and higher cortisol levels are associated with worsening cognition among older adults.[584–586] In contrast, a longitudinal study of 52 older adults found that higher cortisol levels were associated with slower cognitive decline in those with MCI but not in those with normal cognition.[587] Cortisol is known to be susceptible to considerable fluctuations throughout the day,[588] whereby cortisol levels increase upon waking, then steadily decline throughout the day.[589] This difficulty in measuring cortisol levels may explain some of the discrepancies in the aforementioned studies.

Exercise can downgrade the stress response in individuals of all ages by regulating the release of catecholamines and cortisol.[590] During exercise, the HPA axis is activated, and there is a subsequent increase in tissue sensitivity to circulating glucocorticoids.[591] This action buffers the inflammatory processes in the muscle and cytokine production, thereby reducing exercise-induced inflammation.[591] A review of 8 interventional studies evaluating chronic RE and combined interventions in older adults revealed a reduction in serum cortisol over time in four studies; however, many of the included studies lacked a control group, were not randomized, and measured only morning cortisol levels.[580]

There is evidence that mind-body exercise has a down-regulating effect on the sympathetic nervous system and the HPA axis.[592] A systematic review of 25 RCTs in individuals with and without chronic diseases revealed that yoga interventions improved sympathetic nervous system and HPA regulation (using measures of cortisol, heart rate, and blood pressure) compared to controls, however, this review was not conducted on older adults.[590] A meta-analytic review of 40 interventional studies (the majority of participants were older adults) found that Tai Chi has positive effects on both anxiety and depression.[593] A cross-sectional study of 42 middle-aged and older adults revealed that people who practiced Tai Chi and yoga demonstrated significant improvements in mental health outcomes compared to those who performed AE.[594]

Four meta-analyses have found beneficial effects of mind-body exercise on cognition among older adults.[511,514–516] While the mechanism is currently unknown, it is possible that yoga and Tai Chi can contribute to dominance of the parasympathetic nervous system,[592,595] which may improve cognitive performance.[596] An RCT of 118 older adults investigated this theory with an 8-week yoga intervention, after which yoga participants demonstrated improved executive function and an attenuated cortisol response compared to those in the control group.[596] Importantly, the change in self-reported anxiety and cortisol levels predicted performance on the executive function tasks, indicating that downgrading the HPA response is potentially a mechanism by which mind-body exercise improves cognition among older adults.[596] This is the only known study to evaluate the potential of the HPA axis as a mediator in cognitive performance improvements among older adults to date.

Mind-body exercise is an effective intervention for improving cognition among older adults, possibly by reducing stress levels and restoring parasympathetic-sympathetic nervous system balance. While this evidence is encouraging, this topic has only begun to be studied. Mediational RCTs and meta-analyses examining these outcomes are needed to examine the relationship between mind-body exercise, the HPA axis, and cognitive function among older adults.

Exercise Prescriptions to Improve Cognitive Health in Older Adults

Currently there are no exercise guidelines that specifically target cognitive gains in older adults, but clues can be gleaned from the literature on exercise-induced cognitive change. Factors related to an exercise program – exercise type, intensity, session duration and frequency, and program duration – may determine the extent to which exercise impacts cognition. In terms of *exercise type*, most investigations have focused on the effectiveness of AE[484,509–512] although RE[456,511,512] and mind-body exercise[514–516] such as Tai Chi and yoga have shown to be effective in improving cognition among older adults. Some trials have reported beneficial effects of combined AE and RE exercise.[533,554] Colcombe and Kramer (2003) concluded in their meta-analysis of 18 RCTs in sedentary older adults that combined RE and AE yielded larger effects on cognition compared to AE alone or no exercise.[509]

Similarly, Barha and colleagues (2017) discovered in their meta-analysis of healthy older adults that combined training benefitted global cognitive function and episodic memory more than AE and RE alone.[512] *We conclude that single exercise modes are effective in inducing improvements in cognition among older adults, but combined modes may offer additional cognitive benefits.*

Exercise *frequency* also appears to be an important predictor of cognition. Northey et al. (2018) performed a moderator analysis within their meta-analysis and determined that more frequent (5-7 sessions per week) exercise of all types was more beneficial for cognition than less frequent (≤2) or moderately-frequent (3–4) exercise in older adults.[511] These findings are disputed by those of Sanders and colleagues (2019), who revealed that exercise frequency (and in fact, all dose parameters) did not predict changes in cognition among older adults.[518] However, as previously mentioned, Sanders and colleagues excluded many studies where the exercise dose was increased over time.[518] As such, their results may not be applicable to the majority of exercise programs where it is recommended to progressively increase the exercise dose over time. *We therefore conclude that older adults may experience cognitive benefits from exercise 5-7 times per week.*

Exercise *intensity* may be a significant predictor of cognitive benefit.[529,597] In their meta-analysis of 36 RCTs, Northey et al. (2018) performed a moderator analysis of exercise intensity, and determined that high- and moderate-intensity exercise of all types were superior to low-intensity exercise in terms of cognition in older adults; however, the effect sizes were small.[511] In contrast, other evidence indicates that improvements in fitness levels are not required to improve cognition among older adults.[509,520,577] Moreover, improvements in cognition have been obtained using low-intensity exercise, such as Tai Chi[514–516] and yoga.[517] *As such, we conclude that exercise at any intensity may benefit cognition in older adults.*

Longitudinal studies have reported that *exercise session duration* may be an important predictor of cognition among older adults.[507,508] This is supported by evidence from the meta-analysis by Northey et al. (2018), who determined that sessions lasting 45 minutes or longer were more beneficial for cognitive performance than shorter sessions.[511] An RCT conducted with four groups of older adults (controls, 50%, 100%, or 150% of the recommended dose of 150 minutes per week) who performed AE of progressive intensities for 26 weeks revealed that a change in fitness mediated the effect of session duration on visuospatial performance.[492] A dose-response was apparent, with longer session durations enhancing improvements in visuospatial function.[492] *We conclude that exercise sessions for older adults should ideally last 45 minutes or longer.*

In relation to *exercise program duration*, some investigators argue that cognitive improvements may not be apparent until 6 months[513] or a year of exercise training,[491] while other studies have reported positive results in as little as 8,[598] 12,[573,599] or 16 weeks.[533] A 2018 systematic review of 98 RCTs of older adults with and without cognitive impairment determined in their analysis of optimal exercise dose that exercising for at least 52 total hours was associated with improved cognition.[600] Further, their bivariate correlation analysis revealed that the most important predictor of improved cognition was total intervention duration.[600] In contrast, the meta-analysis by Northey and colleagues (2018) revealed similar effect sizes for programs of short (4-12 weeks), medium (13-26 weeks), and long (>26 weeks) durations.[511] It is important to note that the effect of exercise program duration on cognition could be influenced by the frequency of exercise sessions and exercise session duration, as discussed by Sanders and colleagues (2019), therefore it may be more valuable to look at total exercise dose. *As such, we conclude that exercise interventions for older adults have a total duration of at least 52 hours.*

Conclusion and Areas for Future Inquiry

The present paper has provided a review of the literature regarding the effect of exercise on cognition, and an overview of the likely mechanisms underlying this interaction. The evidence indicates that physical activity, notably multimodal and mind-body exercise, offers benefits to cognition in older individuals. The mechanisms underlying these benefits are numerous and overlapping. However, there are many gaps in the literature, such as a lack of high-quality studies evaluating moderators of cognitive function among older adults. Future research using is needed to determine optimal exercise parameters aimed at improving cognition in this population.

Chapter 7- Effect of Exercise on Physical Impairments among People Living with HIV

Background

Chapter 3 outlined the common HIV-associated physical impairments (sarcopenia, gait, balance, aerobic capacity, and frailty) and possible mechanisms underlying these impairments. This purposes of this chapter are to (i) review the available literature evaluating the effect of different modes of exercise training (i.e., aerobic, resistance, combination of aerobic and resistance, balance training, mind-body) on these physical impairments; and (ii) discuss potential mechanisms underlying exercise-induced in these impairments.

Aerobic Exercise

The beneficial effects of aerobic exercise have been well established among PLWH. A 2016 meta-analysis using the Cochrane Collaboration protocol of 24 RCTs concluded that there were significant improvements in maximum oxygen consumption, strength, and body composition among PLWH who performed aerobic or combined aerobic and resistance exercise compared with non-exercising controls.[601] A pilot RCT of 22 older male PLWH evaluated the impact of a 16-week moderate- and high-intensity aerobic exercise program and observed similar improvements on the six-minute walk test in both groups, and significantly larger improvements in aerobic capacity among high-intensity exercise participants than the moderate-intensity group.[602] An RCT conducted with 84 older PLWH (79% were female) who performed a home-based aerobic exercise program observed significantly better 6MWT distances, waist to hip ratios, and cardiovascular risk factors when compared with no-exercise controls.[324] Even light aerobic exercise training for four months decreases total abdominal adiposity, total cholesterol, and triglycerides and increases high-density lipoprotein levels among PLWH with lipodystrophy or dyslipidemia.[603]

Combined Aerobic and Resistance Exercise

Combined aerobic and resistance training interventions have also been evaluated with PLWH. A meta-analysis of 7 trials determined that aerobic capacity and knee extensor and elbow flexor strength significantly improved among PLWH who performed combined aerobic and resistance exercise compared to controls.[604] Another meta-analysis by Chaparro and colleagues (2018) of 13 RCTs concluded that resistance training in isolation and combined with aerobic exercise had a positive effect on both upper and lower body muscle strength among PLWH.[605] Finally, another meta-analysis of 28 studies observed a significant effect of both aerobic and combined aerobic and resistance exercise interventions on exercise capacity (as measured by VO2max) and endurance (using the 6-minute walk test) among PLWH.[606] Of note, combined interventions were associated with larger improvements in aerobic capacity than single-modality exercise interventions. Short-duration combined exercise interventions can also improve body composition; an RCT by Dudgeon and colleagues determined that a 6-week moderate-intensity combined aerobic and resistance training intervention decreased trunk fat and total fat while increasing lean tissue mass among male PLWH.[494]

There is encouraging evidence that PLWH can benefit from high-intensity exercise. O'Brien and colleagues determined in their meta-analysis that higher-intensity aerobic and combined interventions had larger improvements in maximal oxygen consumption than moderate-intensity interventions.[601] Erlandson and colleagues (2018) conducted an RCT with older PLWH (88% male) and healthy controls (95% male) who performed moderate-intensity combined aerobic and resistance exercise three times per week for 12 weeks, then randomized participants to either continue with the same intensity or to progress to a high-intensity program for 12 more weeks.[243] Among PLWH who performed both moderate- and high-intensity exercise, both groups significantly lowered their chair rise time, a measure of lower-extremity strength and mobility.[243] Of note, PLWH had significantly larger improvements in aerobic capacity during the first phase of the study and larger improvements in both the stair climb and 400-meter walk time during the second phase of the study compared to controls.[243] Further, PLWH who performed high-intensity exercise had larger strength gains than PLWH in the moderate-intensity group, while this response was not observed among HIV-negative controls.[243] This research indicates that PLWH may benefit more from high-intensity interventions than HIV-negative individuals.

Resistance Exercise

Robust evidence supports the effectiveness of resistance exercise interventions to improve strength among PLWH. Two meta-analyses have been conducted to evaluate the effect of resistance training on physical performance among PLWH. Poton and colleagues' (2017) meta-analysis of 13 trials determined that resistance training interventions increased muscle strength by 35.5% but not lean body mass.[607] Their results determined that strength gains are maximized among PLWH when resistance training interventions include 5-11 exercises with 3-4 sets of 4-15 repetitions at 60-90% of 1-repetition maximum and are performed three times weekly.[607] O'Brien and colleagues

(2017) also performed a meta-analysis of 20 RCTs with PLWH and determined that resistance training performed three days per week or more for four weeks in total resulted in significant upper and lower extremity strength and body composition (body weight, leg muscle area, and arm and leg girth) improvements.[323] However, they noted no improvements in lean body mass with resistance training and combined resistance and aerobic training in this population.[323]

There is some evidence to indicate that individuals with and without HIV-associated muscle wasting can make improvements in strength and body composition with resistance training. A pre-post observational study of 6 male PLWH with muscle wasting and 19 (14 male, 5 female) PLWH without wasting who performed progressive resistance training 3 times per week for 8 weeks followed by 8 weeks of regular activity revealed significant improvements in strength and lean body mass in individuals with and without wasting following the intervention.[608] Of note, self-reported physical function as measured using the MOS-HIV physical function subscale also improved significantly among the participants with wasting but not those without wasting.[608] This research indicates that PLWH with and without muscle wasting can benefit from progressive resistance training.

Balance Training

Only one known study has evaluated the impact of balance training among PLWH. A single-group observational study conducted with 10 PLWH evaluated the effect of twice-weekly game-based training for six weeks aimed at improving balance and gait.[327] The investigators observed significant improvements in center of mass sway during the semi-tandem test with eyes closed and gait speed during a dual task (which involved counting backwards by 1 while walking 10 metres).[327] Unfortunately, the authors did not identify the sex or gender of the participants.[327] More research is needed to evaluate the effect of balance training on balance performance in this population.

Mind-Body Exercise

There is very little literature evaluating the effect of mind-body exercise on physical performance among PLWH. Kietrys and colleagues (2018) conducted a case-series study of 3 male PLWH with distal sensory polyneuropathy and noted improvements in gait performance such as stride length, step length, stride velocity, walking velocity, and double-limb support time following a 90-minute, twice-weekly yoga intervention lasting 4 weeks among all 3 participants.[328] They also observed improvements in balance performance using the Multidirectional Reach Test in 2 of the 3 participants.[328] However, the participants demonstrated variable performance at follow-up 4 weeks later.[328] Galantino and colleagues (2005) conducted an RCT with two intervention groups (aerobic exercise and Tai Chi) and a control group with male participants with advanced HIV.[434] They observed significant improvements in functional reach performance in both intervention groups.[434] Other than these two studies, no other known research has evaluated the impact of mind-body exercise on physical performance measures among PLWH. This represents a significant gap in the literature to date.

Potential Mechanisms Underlying Exercise-Induced Changes in Physical Performance

There are numerous mechanisms that may explain improved physical performance among PLWH with exercise interventions, including reduced reactive oxygen species and inflammation, decreased cortisol, improved immune function, and the reduction of cardiovascular and metabolic risk factors.

Inflammation and Reactive Oxygen Species

In their meta-analysis of 13 RCTs, Chaparro and colleagues (2018) indicated that aerobic and resistance exercise lowered Interleukin (IL)-6 levels among PLWH but had no change in IL-1βeta.[605] In contrast, another meta-analysis of 23 RCTs conducted by Ibeneme and colleagues (2019) demonstrated no significant improvement in inflammatory markers (IL-6 or IL-1βeta) following aerobic or combined aerobic and resistance exercise interventions among PLWH.[609] This discrepancy in findings may be attributable to the fact that Ibeneme and colleagues (2019) included an RCT where the intervention groups performed only three exercise bouts and this study was not included by Chaparro et al. (2018). By comparison, Chaparro et al. (2018) included two RCTs with interventions lasting 6-weeks[494] and 12-weeks,[610] respectively, in their meta-analysis of IL-6 levels. Furthermore, the meta-analysis by Ibeneme et al. approached significance ($p = .05$) for the effect of combined exercise interventions on IL-6 levels.[609] Considering the available evidence, it appears that combined exercise interventions may be associated with a reduction in some inflammatory markers among PLWH.

An RCT of 30 PLWH (n = 17 males, n = 13 females) that was included in the aforementioned meta-analyses determined that 12 weeks of non-linear resistance training (which involves varying training intensity and volume within each week) improved blood concentrations of IL-1βeta, IL-6, IL-8, and tumour necrosis factor (TNF)-alpha among exercise participants compared to controls.[610] The authors of this study also found an association between adiposity and pro-inflammatory cytokines, whereby a reduction in inflammatory markers was observed with a corresponding decrease in adipose tissue in their sample.[610] This provides evidence that changes in body composition can help reduce markers of inflammation among PLWH who perform non-linear resistance training.

It is also thought that aerobic and resistance exercise training reduces the expression of toll-like receptors in monocytes and macrophages, which can diminish the proliferation of inflammatory markers in adipose tissue, and decrease the secretion of other pro-inflammatory substances.[611–613] Aerobic and resistance exercise enhances and regulates macrophage, neutrophil, natural killer cell, lymphokine-activated killer cell, and cytokine activity, which contributes to decreased inflammation and improved immune function.[614] Exercise interventions may also remove reactive oxygen species which assists antioxidant system modulation.[615] Taken together, there is some evidence that exercise reduces inflammation and reactive oxygen species among PLWH.

Cortisol

Cortisol, a catabolic hormone that increases protein breakdown and reduces protein synthesis in skeletal muscle, is elevated among PLWH,[616,617] although there are issues with cortisol measurement due to diurnal variation.[589] A cross-sectional study of 126 PLWH (83% were male) and 191 HIV-negative controls (46% were male) determined that PLWH had significantly higher mean hair cortisol levels compared to controls.[616] Exercise training may reduce cortisol levels among PLWH. A combined aerobic and resistance training intervention performed by male PLWH lasting 6 weeks reduced waking cortisol levels among exercisers relative to controls.[494] However, more research is needed to confirm these findings.

Cardiometabolic Function

One of the prominent theories explaining improvements in physical function with exercise interventions among PLWH is the reduction of cardiovascular risk factors such as high blood pressure and glucose resistance. A nested analysis of 147 PLWH (80% male) enrolled in an RCT determined that moderate-intensity physical activity levels at baseline were associated with lower IL-6 and C-reactive protein (CRP) levels, and moderate to high intensity physical activity was related to lower body mass index and improved vascular dilation, insulin resistance, leptin, and pericardial fat.[618] Over four time points, median physical activity levels were related to cardiovascular and inflammatory factors such as carotid distensibility, pericardial fat volume, and IL-6.[618] This evidence indicates that physical activity is associated with improved cardiovascular health among PLWH.

There is also some meta-analytic evidence to indicate that exercise improves cardiovascular health among PLWH. Zech and colleagues (2019) performed a subgroup analysis for combined aerobic and resistance exercise and revealed a significant overall effect on resting heart rate.[606] However, they found no significant overall effect of exercise training on systolic blood pressure, diastolic blood pressure, and maximal heart rate.[606]

Regarding RCT evidence of the impact of exercise on metabolic health among PLWH, the results are more nuanced. Zanetti and colleagues conducted an RCT (n = 17 males, n = 13 females) and observed improvements in lean body mass, body fat mass, body fat percentage, total cholesterol, triglycerides, CRP, low-density lipoproteins, and high-density lipoproteins among PLWH who performed non-linear resistance training for 12 weeks.[610] An RCT of a 16-week combined training program did not affect lipid levels, blood pressure, or central visceral fat among female PLWH despite improvements in maximal oxygen consumption and strength.[619] Similarly, a 16-week combined moderate-intensity aerobic and resistance training intervention conducted with PLWH (n = 23 females, n = 18 males) decreased body fat, but did not improve lipid profiles, adiponectin, leptin, or CRP levels.[620] PLWH with lipodystrophy, however, had larger reductions in central obesity when compared with PLWH without lipodystrophy following the intervention.[620] Another RCT with 60% female PLWH had similar results with a 6-month aerobic exercise intervention that reduced total cholesterol, triglycerides, and glucose levels among PLWH with lipodystrophy.[621] These findings indicate that exercise training may induce larger changes in metabolic indices in PLWH with lipodystrophy than those without body fat redistribution.

Very little research has evaluated the impact of mind body exercise on cardiovascular and metabolic disease risk factors among PLWH. Among HIV-negative individuals, yoga interventions have been shown to improve cardiovascular risk factors such as obesity, blood pressure, glucose and cholesterol levels, and vascular function.[595,622] There is some preliminary evidence to indicate that yoga improves blood pressure among PLWH. An RCT conducted with 60 PLWH (29% were women) with mild to moderate cardiovascular disease risk factors who performed yoga for twenty weeks demonstrated significant improvements in resting systolic and diastolic blood pressures compared to usual care controls.[623] In the same study, body weight, fat mass, lipids, and glucose tolerance did not improve among yoga participants, indicating that yoga directly affects blood pressure without modifying other cardiovascular risk factors.[623] These results should be interpreted with caution, as these findings contrast with those among HIV-negative individuals where cardiovascular and metabolic risk factors are both altered by yoga participation.[595,622,624] Clearly, more research is required to determine the effect of yoga on cardiovascular and metabolic health among PLWH.

Immune and Virological Function

The conventional theory has been that CD4+ count and viral load do not increase following aerobic and resistance exercise training interventions. Two meta-analytic studies conducted by O'Brien and colleagues (2016 and 2017) found no effect on CD4+ count and viral load following aerobic and resistance exercise interventions.[323,601] In contrast, the meta-analysis conducted by Poton and colleagues (2017) determined that CD4+ cell count increased by 26% among those who performed resistance training when they evaluated 8 RCTs conducted with PLWH.[607] O'Brien and colleagues (2017) performed four meta-analyses evaluating the effect of resistance training on CD4+ count, revealing non-significant results in two analyses, a negative effect of resistance training in combination with anabolic steroids, and a positive effect of resistance training alone or in combination with aerobic exercise.[323] However, one of the aforementioned analyses included two studies evaluating combined resistance training with anabolic steroid supplementation, revealing an overall decrease in CD4+ following the intervention.[625,626]

In their RCT, Zanetti and colleagues (2016) observed improvements in CD4+ and CD8+ cell counts in addition to enhanced muscle strength and IL-10 levels in their non-linear resistance training group relative to controls.[610] This evidence indicates that resistance training may improve immune function among PLWH. More research is needed to confirm these findings.

Regarding the impact of yoga interventions on immune function, a meta-analysis of 7 randomized studies among PLWH determined that yoga interventions did not improve CD4+ cell counts relative to controls.[627] Only one known study evaluating yoga interventions measured viral load, in which there was no change among yoga participants.[623] A non-randomized study with a comparison group (female PLWH = 2, male PLWH = 32) determined that a 8-week mindfulness-based stress reduction and yoga intervention resulted in within- and between-group increases in both the number and activity of natural killer cells in the intervention group, indicating that mindfulness and yoga may benefit immune function among PLWH.[628] Natural killer cells are important for both viral suppression and protection from opportunistic infections.[629] More research is needed to evaluate the role of mind-body exercise in improving immune and virological parameters among PLWH.

Moderators of Strength Gains among People Living with HIV

Poton and colleagues (2017) performed a meta-regression analysis to determine moderators of strength gains in the HIV population; their findings indicated that training time, cART treatment duration, and study quality were significant moderators of effect sizes related to muscle strength.[607] Importantly, participants treated with cART for 12 weeks or more had almost a 60% increase in strength while those treated for less than 6 weeks had only 37% improvements in strength.[607] The authors of that study theorized that cART may modulate the effect of inflammatory markers in the setting of HIV. To date, this is the only known study to evaluate the potential moderating effect of cART on strength gains in the HIV population.

Conclusion

Clear emerging evidence is indicating that aerobic exercise has benefits for aerobic capacity and cardiovascular health among PLWH, with higher-intensity interventions producing larger gains in aerobic performance. Resistance training has an effect on strength and function in this population as well. Very little evidence has evaluated mind-body and balance interventions among PLWH, but the literature to date is promising. The mechanisms underlying these improvements in physical performance commonly cited in the literature include the reduction of inflammation and cardiovascular risk factors. Further research is needed to evaluate the impact of exercise training on cortisol and immune function in PLWH.

Chapter 8-The Effect of Exercise on Affective Outcomes among People Living with HIV

Introduction

This chapter will review the evidence evaluating the effect of different types of exercise (aerobic, resistance, combined, and mind-body) on mental health, health-related quality of life, and antiretroviral adherence outcomes in this population. This chapter will also identify gaps in the literature and areas for future study.

Mental Health and Exercise

Aerobic, Resistance, and Combined Aerobic and Resistance Exercise

Emerging meta-analytic and systematic review evidence is indicating that aerobic and resistance training provide benefits to mental health among PLWH. A meta-analysis by O'Brien and colleagues (2016) of 24 RCTs (22% female participants) determined that aerobic and combined aerobic and resistance exercise interventions had significant positive effects on depressive symptoms among PLWH.[601] Nosrat and colleagues (2017) performed a systematic review of 52 studies that were not limited by study design or exercise dose and concluded that combined aerobic and resistance exercise have positive separate and combined effects on mental health outcomes among PLWH.[630]

RCT evidence has evaluated the effect of aerobic and resistance exercise on mental health outcomes among PLWH. An RCT that involved 12 weeks of combined aerobic and resistance exercise among female PLWH in Iran observed significant improvement in mental health outcomes including anxiety, social function, depression, and total mental health scores among exercisers compared to controls.[631] Another RCT of 60 adult PLWH (of which 13% were female) determined that 12 weeks of aerobic exercise training resulted in improved depressive symptoms as measured by the CES-D and the POMS overall score and the depression/dejection subscale.[632] In their RCT of 37 male and 12 female PLWH, Jaggers et al. (2015) observed a significant decrease in depressive symptoms and mood disturbances and a significant reduction in salivary cortisol levels among those who had performed combined aerobic and resistance exercise for 6 weeks.[633] Of note, at post-intervention, controls had significantly higher perceived stress levels compared to exercisers, which indicates that exercise may be protective against stress.[633]

Only one known RCT has compared the effect of resistance exercise, aerobic exercise, and stretching control on mental health outcomes among PLWH. Their results indicated that both exercise groups had improved life satisfaction and positive affect, as well as lower negative affect compared to controls, and the aerobic exercise group had significantly higher life satisfaction at study completion than the resistance exercise group.[634] This study has some limitations; it was conducted prior to the introduction of cART in 1996, therefore the confounding effect of these medications cannot be excluded. Furthermore, all of the participants were male and there were more than twice the number of participants with AIDS in the resistance group than the aerobic group.[634] Further research comparing the effect of different exercise types on mental health among PLWH is warranted.

Some research has evaluated the effects of aerobic and resistance exercise on physiological stress markers among PLWH, including blood pressure, heart rate, and cortisol. Exercise training may provide some benefits to physiological stress markers among PLWH. An RCT of 111 male PLWH who underwent moderate-intensity combined aerobic and resistance training for 6 weeks revealed significantly reduced waking cortisol levels among exercisers compared to controls.[494] However, much more research is needed to determine the effect of exercise on cortisol levels among PLWH. Regarding heart rate, Zech and colleagues (2019) determined in their meta-analysis that combined aerobic and resistance exercise had an overall positive effect on resting heart rate among PLWH.[606] They did not find an effect of exercise training on systolic blood pressure, diastolic blood pressure, or maximal heart rate.[606]

Mind-Body Exercise

Meta-analytic and RCT evidence indicates that yoga can have benefits on mental health among PLWH. The only known meta-analysis (n = 7) to evaluate the benefits of yoga interventions in this population determined that there were substantial improvements in anxiety (d+ = 0.71), perceived stress (d+ = 0.80), and positive affect (d+ = 0.73) among yoga participants relative to controls.[627] In the same study, the authors concluded that yoga interventions did not improve depression symptoms (d+ = 0.33) or quality of life (d+ = 0.23) among PLWH when compared with controls but there were significant improvements in depressive symptoms among yoga participants over time (d+ = 0.48).[627]

RCT evidence is also demonstrating the benefits of yoga on mental health outcomes among PLWH. A randomized trial of 73 (male n = 50, female n = 21, transgender n = 2) previously-incarcerated PLWH with a history of substance use determined that yoga participants reported lower anxiety levels following the 12-week intervention as measured by the perceived stress scale compared to usual care controls.[635] Yoga participants also reported lower substance use than controls after one month, two months, and three months of the intervention.[635] The authors of the study posited that improved mental health and coping skills in response to anxiety assisted in the modulation of stress responses and may have reduced substance use in their sample.[635]

Very few studies to date have evaluated the effects of mind-body exercise on physiological stress markers among PLWH, including blood pressure, heart rate, and cortisol. Cade et al. (2010) found a reduction in blood pressure among yoga participants,[623] while Mawar and colleagues (2015) did not.[636] Agarwal et al. (2015) observed no change in salivary cortisol following their yoga intervention.[637] More research is needed to determine the effect of mind-body exercise on physiological stress markers in this population.

Health-Related Quality of Life

Effect of Aerobic, Resistance, and Combined Interventions on HRQoL

Meta-analytic and systematic review evidence is pointing to the benefits of aerobic and resistance exercise on HRQoL outcomes among PLWH. O'Brien and colleagues' (2016) meta-analysis of 24 RCTs concluded that aerobic and combined aerobic and resistance exercise interventions had a significant impact on HRQoL among PLWH, as measured by the SF-36.[601] Another meta-analysis conducted by Gomes-Neto and colleagues (2015) evaluated combined aerobic and resistance training interventions (n = 7) and determined that there were significant improvements in health status, energy/vitality, and physical function domains of HRQoL (using the SF-36, WHOQOL-BREF, and MOS-HIV) among PLWH exercisers compared with non-exercising controls.[604]

An earlier systematic review conducted by Gomes-Neto and colleagues (2013) of 29 RCTs evaluated the effect of aerobic, resistance, or combined exercise on physiological and functional outcomes among PLWH.[638] Their results revealed that combined aerobic and resistance training had positive effects on HRQoL using the MOS-HIV, SF-36, and WHOQOL-BREF, but resistance training alone had minimal effects.[638] However, the characteristics of the resistance training studies was underreported; for example, in five of the ten included studies, the duration of exercise sessions was not reported.[638] Furthermore, many of the included studies did not include female participants; six studies included only male participants, and one study included female participants only. More research is needed to determine the effect of unimodal and multimodal types of exercise on HRQoL among PLWH of all genders.

RCT evidence also indicates that unimodal (aerobic or resistance) exercise interventions can have a beneficial effect on HRQoL among PLWH. Agin and colleagues (2001) determined that progressive resistance training for 14 weeks significantly improved physical, general health perceptions, and vitality subscales scores on the MOS-HIV among female PLWH.[639] An RCT of 100 PLWH (60% female) with lipodystrophy determined that aerobic exercise training for 6 months improved among exercisers on the psychological, independence, social relationship, and overall quality of life domains of the WHOQoL-BREF as well as an added cART-specific HRQoL domain compared to controls.[640] There were also gender differences in HRQoL in this sample, whereby female exercises showed significantly greater improvements in the psychological, social relationship, and cART-specific HRQoL domains than males.[640] This evidence indicates that that female PLWH exercisers may experience larger benefits to HRQoL following exercise training than males.

Effect of Mind-Body Interventions on HRQoL

The effect of mind-body exercise on HRQoL has been evaluated among PLWH using evidence from a systematic scoping review and a meta-analysis. A systematic scoping review of 84 studies concluded that mind-body practices had beneficial effects on HRQoL among PLWH.[641] Similarly, a meta-analysis of 7 RCTs reported improved HRQoL among yoga participants at follow-up compared to baseline assessments (d+ = 0.27); however, no significant increases in HRQoL were observed when compared with controls (d+ = 0.23).[627] It is possible that between-group effects of yoga on HRQoL may be detected with longer follow-ups post-intervention, as changes in mental health may be more immediate than HRQoL.[627] Further research could employ the use of longer follow-ups to determine if there are between-group differences in HRQoL following mind-body interventions.

There is some RCT evidence to indicate that HRQoL improves with mind-body interventions. Galantino et al. (2005) conducted an RCT of 38 men with advanced HIV and observed significant improvements in overall quality of life on the MOS-HIV among aerobic exercise and Tai Chi exercisers relative to controls.[434] Another RCT of 61 PLWH (64% female) demonstrated positive effects on overall quality of life, physical, level of independence, and psychological domains as measured using the WHOQOL-HIV BREF following a 12-week meditation, breathing, and chanting intervention (Sudarshan Kriya yoga) compared to controls.[636] However, these results may not generalize well to all PLWH as this study excluded PLWH on cART and the intervention did not include physical poses.[636] Another RCT conducted with 70 cART-untreated PLWH randomized participants to a wait-list control group or a daily 60-minute yoga practice for 3 months and measured HRQoL using the WHOQOL-HIV BREF; however, they did not report demographic information or their HRQoL results and only published a conference poster.[642] Clearly, more RCTs are needed to determine the effect of mind-body interventions on HRQoL among PLWH.

Antiretroviral Adherence

No research to date has evaluated the impact of physical activity on cART adherence in the HIV population but there is some evidence from the longitudinal, cross-sectional, and qualitative literature to indicate that there is a relationship between physical activity and cART adherence. Some research is indicating that physical inactivity is associated with reduced adherence to cART.[643] A recent study with a focus group of mostly male PLWH reported that the same barriers that limit cART adherence such as poor motivation and depression may also limit physical activity participation.[644] Of note, facilitators such as social support may also help promote adherence to both cART and physical activity.[644] Physical activity participation may be associated with improved adherence to cART.[34] Physical activity levels predict a reduction in depressive symptoms,[632,645,646] which in turn predict cART adherence.[34] A large longitudinal study conducted with men who have sex with men determined that physical inactivity was related to cART non-adherence, but when depression was used as a covariate, the relationship became non-significant.[365] The investigators also performed mediational analyses and determined that physical inactivity is related to depression and cART non-adherence, which leads to reduced virological suppression.[365] Taken together, there is some evidence that physical activity is associated with reduced depression, which in turn, promotes cART adherence.

Despite the lack of research evaluating the effect of exercise training on cART adherence, there is some evidence that cognitive-behavioural interventions can improve adherence among PLWH. A crossover RCT (38 male, 7 female participants) with a cognitive-behavioural intervention demonstrated improvements in medication adherence and depression among PLWH after 3 months compared to controls.[647] PLWH (84% of which were male) enrolled in an RCT who performed a mindfulness-based stress reduction intervention did not see improvements in cART adherence but they had a significant reduction in cART-attributable symptom frequency at both three months and six months post-intervention compared to a wait-list control group.[648] It is possible that exercise types with a cognitive component (such as mind-body exercise) may promote cART adherence; further study is needed in this area.

Conclusion

There is strong evidence to indicate that exercise has benefits for affective outcomes such as mental health and health-related quality of life and preliminary evidence regarding its relationship with medication adherence in the HIV population. A small number of studies have evaluated the impact of mind-body exercise on affective outcomes and no studies have evaluated its impact on cART adherence among PLWH. Further research is needed to evaluate the effect of exercise (particularly mind-body) on affective outcomes in this population.

Chapter 9-Using the Theoretical Domains Framework to Identify Barriers and Facilitators to Exercise Among Older Adults Living with HIV

This chapter is a manuscript that was published in *AIDS Care* in July of 2018. This article was a qualitative study undertaken to determine the barriers and facilitators to physical activity among older PLWH in the Halifax area in order to inform our pilot randomized trial.

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Contribution Statement

I developed the interview guide, conducted all 12 interviews, and analyzed the data. I developed and wrote the manuscript with assistance from Dr. Marilyn MacKay-Lyons, Larry Baxter, and Laura Keeler.

Abstract

People with HIV are living longer. However, co-morbidities are often more prevalent and severe than in the general population and have greater impacts on health status. Although compelling evidence exists about the health benefits of exercise in the HIV literature, many people living with HIV tend to be physically inactive. The purpose of this study was to use the Theoretical Domains Framework to investigate the barriers and facilitators to participation in exercise of older people living with HIV. This qualitative study involved in-depth, semi-structured interviews with 12 adults aged 45 years and older recruited from HIV organizations and health centres. Data were analyzed thematically using the Theoretical Domains Framework, and two investigators independently coded transcripts. Six prominent domains were identified from the interviews: Social influences, environmental context and resources, reinforcement, intentions, social and professional role, and knowledge. Themes emerging from the interviews fit into all 14 domains of the Theoretical Domains Framework, and 67% of themes fit into the six most prominent domains. The participants had a working knowledge of exercise and its health benefits but were unfamiliar with specific exercise parameters. The majority identified environmental or resource constraints as salient barriers for participation in exercise programs. Co-morbidities, injuries, and the side effects of HIV disease and medication were also acknowledged as barriers. Stigma and discrimination from friends, family, people within the LGBTQ community, and health care providers were commonly discussed. Participants spoke of the importance of social support to facilitate participation in exercise programs. Other facilitators included using technology and incorporating exercise into day-to-day activities. People aging with HIV experience many barriers to exercise. Those designing exercise interventions for people aging with HIV should incorporate strategies to address these obstacles.

Keywords: HIV; physical activity; barriers; facilitators; implementation science

Background

People living with HIV (PLWH) are living longer due to the advent of combination antiretroviral therapy (cART).[649] However, increased survival is associated with an emerging threat – a higher prevalence and severity of comorbidities than in the general population.[650] PLWH undergo an accelerated aging process,[651] encountering health concerns in terms of osteoporosis,[227] muscle wasting,[652] balance dysfunction,[208] and cognitive deficits.[111,113,653] Physical activity (PA) is recommended to help counteract such issues.[654] Compelling evidence exists for the benefits of exercise on physical and cognitive functions in PLWH.[323,601,604,655,656] The American College of Sports Medicine recommends aerobic exercise 30-60 minutes, 3-5 days per week and resistance training 2-3 times per week at a moderate intensity for PLWH.[519]

Despite acknowledging the benefits of exercise,[657] many PLWH are not meeting current guidelines; for example, only 28% and 19% of PLWH, respectively, met *Healthy People 2010* recommendations for moderate and vigorous PA.[658] PLWH also demonstrate high levels of dropout in exercise trials.[323,472,601] Given that participation in, and adherence to, exercise programs are challenging for PLWH, it is important to understand the facilitators and barriers to changing behavior.

The Theoretical Domains Framework (TDF) helps identify relevant mediating factors of behaviour change that can be targeted using behaviour change techniques.[659] The primary objective of this study was to gain knowledge about PLWHs' barriers and facilitators regarding exercise participation, using the TDF to guide the investigation.

Methods

We followed the TDF-based implementation research process outlined by Atkins et al.[660] A qualitative design with semi-structured interviews was used to explore the lived experiences of older PLWH with exercise, specifically yoga. Ethics approval was obtained from the Nova Scotia Health Authority Research Ethics Board. A committee of 7 PLWH, along with the principal investigator, developed the interview guide. To ensure an in-depth inquiry, questions addressed all 14 TDF domains. The interview guide was piloted to confirm comprehension and question organization. Participants were recruited from numerous community and health organizations with the following inclusion criteria: HIV diagnosis, age 45 and older, and willingness to provide informed consent. In-person interviews were digitally audio-recorded in their entirety and transcribed verbatim. At interview completion, each participant filled out a demographic questionnaire and was given a stipend.

De-identified transcripts were uploaded onto NVivo11 and data were coded according to the 14 TDF domains[659,661] using deductive content analysis.[660] To ensure rigor and comprehensiveness, two independent investigators coded transcripts. Each paragraph has assigned to one or more domain, based on the established definitions of the domains.[660] The two coders met frequently to create a coding guideline[660] and to resolve any disagreements. Participant enrolment was terminated when saturation was achieved, whereby no new themes emerged.

Results

Participants

Table I: Participant characteristics (n=12)	
Sex number (%)	Male: 9 (75%) Female: 3 (25%)
Age mean, years $\pm SD$ **(range)**	56.6± 8.8, (range 45-78 years)
Ethnicity	Caucasian/European: 11 (92%); First Nations: 1 (8%)
Educational level (highest achieved)	Master's degree: 3 Undergraduate/college degree: 3; Some university: 1 Post-secondary course: 1 Grade 12: 3 Grade 11: 1
Employment status	Full time: 5 Part time: 2 Retired: 2 Unable to work: 3
Income ($ range)	<10,000: 2 10,000-19,999: 2 20,000-29,000: 3 30,000-39,999: 1 40,000-49,999: 1 50,000-59,999: 2 >100,000: 1
Years living with HIV (mean $\pm SD$**)**	20.0± 10.0
Taking antiretroviral medication	Yes: 12 No: 0
Viral load	Undetectable (< 50 copies): 12 Detectable: 0
CD4 mean $\pm SD$	811± 394
Self-reported health status	Very good: 5 Good: 6 Neutral: 1 Poor: 0
Self-reported current level of exercise	Very high: 0 High: 7 Moderate: 3 Poor: 2
Self-reported ability to participate in exercise program	Very good: 4 Good: 8 Neutral: 0 Poor: 0

Data saturation was achieved after completing interviews with 12 participants. Participant characteristics are summarized in Table I. The majority identified as male, middle-aged, and Caucasian. All were on antiretroviral medication and had undetectable viral loads. Substantial diversity was found in participants' educational background, employment status, and income. Most were moderately positive about their health status and ability to participate in PA.

Classification of Themes Using the TDF

Operational definitions for TDF domains and coding frequency are provided in Table II. Barrier and motivator themes were most prevalent in six domains (listed by percentage of total codes): social influences (15.4%), reinforcement (12.0%), environmental context/resources (12.0%), intentions (10%), social/professional role and identity (9.2%), and knowledge (8.4%). Overall, themes emerging from the interviews fit into all 14 TDF domains, and 67% of themes fit into the six most prominent domains. Tables III and IV summarize the identified barriers and facilitators to PA.

Table II: Operational definitions of the domains of the Theoretical Domains Framework

Domain	Operational Definition	Coding Frequency (% of total)
Social influences	Effects of others on ability to exercise	320 (15.4%)
Environmental context and resources	Contextual factors (e.g., time, location, money, weather, injuries, medications, comorbidities) that influence ability to exercise	249 (12.0%)
Reinforcement	Perceived incentives of participating in exercise	249 (12.0%)
Intentions	Level of readiness or motivation to exercise	208 (10.0%)
Social/professional role and identity	Personal, inter-personal, and work-related attributes that influence ability to exercise	192 (9.2%)
Knowledge	Understanding of physical activity: its importance, benefits and current exercise guidelines for PLWH	174 (8.4%)
Beliefs and capabilities	Physical, mental, and psychological beliefs about ability to exercise	163 (7.8%)
Beliefs about consequences	Assumptions about of the effects of not exercising or adopting a healthy lifestyle.	127 (6.1%)
Optimism	Confidence about health status and ability to maintain their current level of activity	102 (4.9%)
Goals	Objectives of participating in exercise	75 (3.6%)
Emotion	Affective factors that influence ability to exercise	73 (3.5%)
Behavioural regulation	Ability to develop and maintain an exercise routine	65 (3.1%)
Skills	Techniques and abilities required to participate in exercise programs	50 (2.4%)
Memory, attention, decision processes	Influence of current cognitive status on ability to exercise	34 (1.6%)

S*ocial influences* interfered with some participants' ability to exercise, particularly among the three female participants, and included stigma and discrimination from friends, family, LGBTQ community members, and health care providers. *Social influences* motivators included having an exercise partner and receiving encouragement from health care providers. In terms of *environmental context/resources,* most participants referred to the side effects of HIV medications (e.g., fatigue, lipodystrophy), other comorbidities, and lack of money or exercise facilities as barriers to PA. Symptoms of fatigue, burn-out, and reduced self-efficacy were often noted as negative factors affecting participants' *intention*s to exercise**.** Many participants identified lack of motivation as a barrier. Many forms of *reinforcement* were perceived as PA facilitators - physical and mental benefits, encouragement from others, and use of technology for monitoring activity were enablers.

Most felt their *social/professional role* was a barrier as the HIV community was not cohesive or they were not actively engaged in the HIV community. Conversely, some participants thought their HIV status was a part of their identity, which motivated them to exercise. Participants had a lack of *knowledge* of specific exercise types and parameters, or were not provided with dosage recommendations from their physicians. The participants had a working knowledge of exercise and its health benefits; however, most were unfamiliar or had misconceptions about yoga. *Beliefs about capabilities* regarding yoga included lack of familiarity and concerns about physical limitations.

TABLE III: BARRIERS TO PARTICIPATION IN PHYSICAL ACTIVITY AND EXERCISE

TDF DOMAIN	Common themes	Quotation(s)
KNOWLEDGE	•Lack of information from health care providers/ community •Unfamiliar with yoga	"I've never read anything on yoga. No one's ever explained anything to me about yoga. So I'm pretty well in the dark about it." P002 "We have all these wonderful programs sometimes but they don't really advertise things. So people don't understand or don't know." P006
SKILLS	•Pacing •Using exercise equipment correctly	"You've got to know your limits, you've got to know what you can lift, you've got to know the machines." P002 "… if they want to go lift weights, for example, some people don't know how to work the machines. Or if it's a yoga class, a lot of that requires some skill to learn how to do the poses and things like that." P007
SOCIAL/ PROFESSIONAL ROLE/IDENTITY	•Lack of cohesiveness of HIV community	"The gay community here is small, and the HIV population is very small. Even though I'm undetectable, people just, you know, hear the 3 letters and, you know, it's a bad thing." P003
BELIEFS ABOUT CAPABILITIES	•Lack of flexibility, coordination, and balance •Poor self efficacy	"Yoga is people stretching and going into all sorts of weird positions on a mat. But I've never tried and I know it would be challenging for me because I'm not a very flexible person… I'm not a very coordinated or flexible person. And I guess the older I get, the less I do those things, the more I become inflexible and uncoordinated." P008
BELIEFS ABOUT CONSEQUENCES	•Fear of injury	"Well, to be totally honest, at my age, I'm 62, an injury now could be the last injury. Because at my age, your body don't heal like it used to when you were young. And I mean you could, and you were up the next day, right. But as you get older, it's a longer process, right. So I really have to, how can I say this, get my insides to match my outsides." P007
INTENTIONS	•Lack of internal motivation	"I think, oh, I want to do it, I want to look good, you know, I want to start getting out again and doing social things instead of just being here all the time. But it's just the motivation isn't there sometimes. Now, I say I'm going to run, run, run in a couple more weeks. Am I? Or am I just saying it?" P002
MEMORY, ATTENTION, DECISION PROCESSES	•Adverse effects of cognitive problems on exercising	"If I had to memorize a routine to follow, that would be challenging if I didn't have it… If I wasn't following someone or had sort of a cue card or something." P008
ENVIRONMENTAL CONTEXT/ RESOURCES	•Weather, cost, lack of facility •HIV medications, side effects •Comorbidities and injuries	"Sometimes it does because, well, you could wake up today and feel great, and tomorrow you could be pretty near dead. So I don't know, one day you're good, and the next day you're half-dead." P005
SOCIAL INFLUENCES	•Stigma and discrimination	"… I think stigma towards people who are HIV positive, it comes in all flavours and colours. And sometimes it's really overt and like a message when you're chatting with somebody. Like, 'Oh, I don't want to meet you because you're HIV positive.'…So yeah, there are very direct experiences of stigma. And painfully as it is to say it, directed at me from my 'own' community" P11
EMOTION	•Anxiety and depression •Burn-out •Fear	"If you're not emotionally in a good place, you know, you say, 'Ah, not today'. Then one day turns into two, two days turns into three. The next thing, you're not exercising anymore. That's kind of what happened to me. So I know it's like a daily process." P007

Facilitator-related themes included *optimism* about their health despite HIV status and co-morbidities, and *beliefs about the consequences* of not being physically active as a motivator to stave off the effects of HIV, comorbidities, and aging. Regarding *behavioural regulation*, participants talked about using goal-setting techniques and routine development, while others discussed using PA as a form of transportation to facilitate participation. Feelings of anxiety, depression, and burn-out *(emotion*) were occasionally discussed during the interviews. Some participants indicated that PA participation was precluded by a poor state of mental health.

Table IV: Facilitators to participation in physical activity and exercise

TDF Domain	Themes	Quotation(s)
Social/ professional role/identity	•HIV diagnosis has reinforced positive •Identity as a person living with HIV	"So I work in a field where I'm always trying to externalize things, right. So rather than people seeing themselves as the problem, I'm trying to help them to see the problem as the problem, not the person as the problem… So I say I'm HIV positive. But then that's like so connected to me… So I say it that way but I like to think that I say that HIV is a part of me. So it's like on my days when I'm feeling really healthy about my relationship with it, it's like yeah, it's a component of who I am but it's not the be all and end all of who I am. But there's a bit of a language thing there, right…You know, like there's the whole like I'm living with HIV. Which sounds strange to me. Like we're cohabitating." P11
Optimism	•Confidence in maintaining/initiating new exercise routine •Positive health outlook	"Like there's times I do self-talk and I say to myself, oh, what's the use? You know, you've got HIV anyway. What's the use? And then the conversation starts – the good. Well, you've got to stay strong and… You know what I mean? You can't let the disease defeat you, right. You've got to put up a good fight." P007
Beliefs about consequences	•Mitigating the effects of HIV, medications, comorbidities, and aging with exercise	"Oh, I'm going to keep on trying because this getting old sucks. This isn't even an HIV thing. Like this is just the changes in my body are just crazy. And I shouldn't say it's not an HIV thing because we do age quicker with HIV. And I mean I know after my heart thing, they told me my heart was like 15 years older than it should be. So I mean there's a whole bunch of crap going on inside that, you know, needs to be taken care of, I guess. The damage is done but let's just leave it at this. And if I can do a bit of exercise, you know, maybe the progression won't be as quick." P001
Reinforcement	•Physical/mental benefits •Encouragement from friends/health providers •Use of technology	"Well, you look better, you feel better. You know, more physical exertion during the day, you get a better night's sleep. I'm probably less moody at work if I've had that one hour in the morning to, you know, do whatever, to kind of clear my mind. Even if it's just go for a run or do something. So I would say overall it makes you a better person." P003
Intentions	•Prioritizing exercise over other activities	"You know, living with HIV all this time, and even my peers and people close to me, I've had arguments about what are priorities. And me, for me my priority is my health. And it always has been from the day I got sick. To the point of whatever I need to do. I mean I would never hurt anyone or steal from anyone. But it means staying on a disability. Where I could have been a little more ambitious and maybe challenged myself a little bit more that way. But instead, I would work out more, and focus more, and meditate more, and do more yoga, and the things that were sort of more inside to keep me strong. " P009
Goals	•Weight loss •Social interaction •Better health	"So the motivators are I'd say it's about trying to maintain for as long as I can my ability to do what I want to be able to do – in a nutshell. So that's being able to move, to be able to feel healthy, to not have like all sorts of hospital stays, and, you know, just to feel good." P11
Memory, attention, decision processes	•Lack of adverse effects of cognitive problems on exercising	"No, [cognitive problems] affect everything else. But not for me personally. They affect everything else but not [exercise]. " P009
Social influences	•Encouragement from friends •Encouragement from health care providers	"I try to associate with as many positive people as I can. I mean I don't mean HIV positive, I mean positive people...And I have to know who they are, and what they're about, and what their values are, and their belief system. You have to eat healthy, you have to sleep healthy, you have to have a good circle of a friends and a good support system." P004
Behavioural regulation	•Developing a routine •Combining exercise with other behaviours	"I've always been a very physically active person. I ride my bike almost every day. It's how I get to work. I don't have a car. I use a bicycle. And when I can't a bicycle because of weather, I walk or I'm on the bus. I'm not doing any great distances but it's a regular part of my routine." P12

Discussion

This study is the first to our knowledge to apply the TDF to identify barriers and facilitators to PA among older PLWH. Findings from our study are partly aligned with previous research conducted on HIV-specific barriers to PA. Some participants identified social influences as facilitators while others perceived them as barriers. Some related positive experiences with health care providers while others were negatively influenced by stigma within the community. Similarly, PLWH in South Africa indicated that HIV-related stigma adversely affected their engagement in PA.[662] The link between social influences and exercise raised by the participants in our study supports previous accounts of PLWH with higher levels of social support participating more frequently in PA.[658,663] As well, group-based exercise has been found to reduce social isolation and HIV-associated stigma.[664]

Although most of our participants considered the mental and physical benefits of exercise as motivators, they often described physical symptoms such as excessive exertion and fatigue as prohibitive. Recently, Rehm & Konkle-Parker (2016) and Li et al. (2017) also reported these symptoms as barriers to exercise participation among PLWH.[657,665] Preliminary results of another study indicated that a quarter of PLWH identified the problematic side-effects of HIV medications,[666] but medication-related symptoms were not identified as a significant barrier to PA as we found in this study.

The lack of self-efficacy identified as a barrier to PA is of concern because self-efficacy is regarded as a significant predictor of adherence to PA among PLWH.[667] In fact, psychological attributes, such as attitudes toward exercise and self-efficacy, may be more influential mediators of PA adherence than physical characteristics.[668] Most participants in our study spoke of the mental and physical benefits as motivators to PA. However, many were not receiving advice about PA parameters from health care providers. To address this barrier, we recommend that health care providers offer basic exercise prescriptions to their patients, particularly resistance and balance exercise, since osteoporosis and balance impairments are common among PLWH.[208,251,254] Participants' lack of knowledge regarding PA in this study also highlights the role of physical and occupational therapists in the rehabilitation cascade for PLWH.

In their study, Li and colleagues (2017) identified barriers to PA and made recommendations for exercise interventions for PLWH, including offering affordable group interventions to promote social interaction, providing self-management programs to promote self-efficacy, and flexible exercise sessions to account for the episodic nature of HIV.[665] Such strategies should be implemented to increase access and participation in PA among aging PLWH.

Conclusion

PLWH experience numerous barriers to PA but also identify many facilitators to motivate engagement. Researchers and clinicians designing exercise interventions for PLWHs should incorporate strategies to address these obstacles.

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Conflict of Interest

The authors declare no conflicts of interest.

Chapter 10-Evaluating the Feasibility and Impact of a Yoga Intervention on Cognition, Physical Function, Physical Activity, and Affective Outcomes in People Living with HIV: Protocol for a Randomized Pilot Trial

This chapter is a manuscript that was published in *JMIR Research Protocols*. The article outlines the protocol for the randomized pilot trial, including the study methods, outcome measures, and data analysis plan. The results of this study are described in chapter 11.

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Contribution Statement

I developed the protocol with assistance from Dr. Marilyn MacKay-Lyons, Dr. Kelly K. O'Brien, Dr. Marie-Josee Brouillette, and Dr. Jaqueline Gahagan. I also drafted the manuscript and received edits from the co-authors.

Abstract

Background: Despite lower mortality rates due to combination antiretroviral therapy, people living with HIV are now grappling with increasingly complex health issues, including cognitive impairments in such areas as memory, attention, processing speed, and motor function. Yoga has been shown to be an effective form of exercise and mindfulness-based stress reduction for many clinical populations. However, no randomized trials have evaluated the impact of yoga on cognitive and physical function among people living with HIV. Objectives: The purpose of this pilot randomized trial is to determine the feasibility of a yoga intervention in order to lay the groundwork for a full-scale, multi-site, community-based trial for people living with HIV. Specific objectives are to: **1)** Assess the feasibility of the study protocol and procedures; **2)** Compare cognitive function in the yoga intervention group to the usual care control group after 12 weeks of the intervention in people living with HIV; and **3)** Compare the effects of the 12-week yoga intervention versus control on balance, walking speed, physical activity, mental health, medication adherence, and quality of life in people living with HIV. Methods: We propose a pilot randomized trial with two parallel groups comparing yoga versus control. We will recruit 25 people living with HIV (≥35 years) from community and health organizations in Halifax, Nova Scotia, Canada. After baseline assessment with blinded assessors, participants will be randomly assigned to the yoga or control group using a random computer generator. Participants in the yoga group will engage in supervised 60-minute group-based yoga sessions 3 times weekly for 12 weeks at a yoga studio. Participants in the control group will maintain their current physical activity levels throughout the study. Results: As per the CONSORT extension for pilot studies, means of all outcomes, mean change, and 95% confidence intervals will be calculated for each group separately. Independent t-tests and Fisher exact tests will be used to compare the two groups at baseline. We will analyze quantitative post-intervention questionnaire responses using Chi-square tests, and open-ended responses will be analyzed thematically. Intention-to-treat and per-protocol analyses will be used in the analysis of the secondary variables. Changes in outcome variables will be examined between groups and within groups. Effect sizes will be reported for each outcome. A priori adherence and satisfaction criteria will be met if participants attend ≥70% of the yoga sessions and if ≥70% are satisfied with the intervention as determined by a post-participation questionnaire. Conclusions: This pilot randomized trial will be the first to investigate the feasibility and effect of a yoga intervention on cognitive and physical outcomes in people living with HIV. This work will inform the feasibility of further investigation in terms of capacity-building, participant recruitment and retention, and assessment and intervention protocols.

Trial registration: ClinicalTrials.gov identifier: NCT03071562
https://clinicaltrials.gov/ct2/show/NCT03071562?term=NCT03071562&rank=1

Trial funding: Canadian Institutes of Health Research Catalyst Grant in HIV/AIDS Community Based Research

Keywords: HIV, AIDS, yoga, cognition, balance

Introduction

Cognitive Impairment in People Living with HIV

Despite lower mortality rates due to combination antiretroviral therapy (cART), people living with HIV (PLWH) are now grappling with increasingly complex health issues,[669] including cognitive impairments in such areas as memory, attention, processing speed, and motor function.[74] Even with the widespread use of cART, 30-60% of PLWH experience cognitive impairment.[74,449] Given that the number of people with HIV-associated cognitive impairment is expected to increase 5 to 10-fold by the year 2030,[52] and the incidence of HIV infection is increasing among older adults,[117] this issue has become a public health concern.[118]

Aging and HIV appear to have combined deleterious effects on both brain structure and function, and some investigators have hypothesized that these effects could be synergistic.[110,111] As such, the combined effect of age and cognitive impairment in HIV has become a concern over the past decade, especially as PLWH now have a life-expectancy that rivals that of their HIV-negative counterparts.[109] Proposed mechanisms for cognitive dysfunction include direct attacks of the virus on brain tissue and indirect processes such as local or systemic inflammation.[670] Glial cells, possible reservoirs for the virus, release pro-inflammatory cytokines and toxins associated with cognitive disorders and neuron degeneration.[123] Protein gp120 damages neurons by causing calcium overload and reducing brain-derived neurotrophic factor, the central growth factor involved in neurogenesis.[105]

HIV-associated cognitive impairment has a profound impact on activities of daily living,[671] social function,[672] quality of life,[181] employment,[57] and adherence to pharmacological[673] and non-pharmacological treatment.[674] Despite the fact that ~95% adherence to cART is required for adequate viral suppression, 66% of participants in a HIV clinical trial “simply forgot” to take their medications.[675] Pharmacological adherence is a major priority, given that cART is the mainstay of proper HIV management. A study of 267 adults with HIV revealed that those with cognitive impairment performed worse on functional laboratory measures of shopping, cooking, finances, medication management, and work-related skills than those with normal cognition.[61] Furthermore, the authors discovered that poor executive function, learning, attention, working memory, and verbal abilities strongly predicted functional performance.[61] Authors of another study revealed that symptomatic cognitive impairment was associated with significantly worse scores in eight domains of the Medical Outcomes Survey for HIV (MOS-HIV).[48] PLWH with cognitive impairment are less likely to be employed,[56] have a difficult time returning to work after disability,[676] and have difficulties adapting to the demands of work.[61]

Gait and Balance Impairments among People Living with HIV

While the cognitive aspects of HIV-associated neurocognitive disorder such as memory, attention, and processing speed have been studied in great detail, the motor aspects have not received much attention. There is evidence of a shared pathology between cognitive and motor functions; a large study of 1,549 PLWH revealed a significant relationship between slowed gait and worsening cognitive function.[93] Balance and gait impairments are common among PLWH[208] and are associated with frailty, higher rates of falls, and increased mortality.[149] Decreased gait speed is linked to higher fall risk, even in those taking cART with undetectable viral loads.[149] A recent systematic review and meta-analysis of 16 cross-sectional studies and one prospective cohort study conducted by Berner and colleagues (2017) evaluated the available literature on gait and balance dysfunction in PLWH;[206] three[209,212,251] of eight studies[149,201,208,209,212,226,251,261] that examined gait speed reported slowing of fast gait speeds among PLWH compared to controls.

Balance performance tests also reveal balance impairments among PLWH. Using the Single Leg Stance Time Test, Bauer and colleagues (2011)[208] revealed a significant decrease in non-preferred single leg stance time among obese PLWH compared to seronegative controls in their sample of 86 seropositive and 121 seronegative individuals. Sullivan and colleagues (2011)[207] had similar findings in their sample of 40 female and male PLWH, but found no differences between groups in tandem stance time. Using the Single Leg Stance Time Test with eyes closed in their sample of 308 PLWH, Tanon and colleagues (2017)[265] determined that 87% of participants demonstrated balance impairments. Performance on the Heel-To-Toe Walk Test with eyes closed,[207] the Limits of Stability Test,[208,226] and the 360-Degree-Turn Test (among PLWH with obesity only)[208] may also be impaired. Notably, PLWH appear to perform well on the Berg Balance Scale,[149,206,227] which indicates that more challenging dynamic balance assessments are required to identify impairments in this population.

Exercise and Cognitive Function in People Living with HIV

Quigley and colleagues (2018) recently published a scoping review to map the available evidence regarding physical activity and cognitive outcomes (both objective and self-reported) among PLWH.[656] The scoping review included 16 studies: five randomized controlled trials (RCTs),[434,467–470] three pre-post single group observational studies,[471–473]and eight cross-sectional studies[150–157] with a total of 1,701 PLWH.[656] The non-interventional research indicated a strong association between physical activity levels and cognitive performance as measured by a cognitive battery in PLWH; all eight cross-sectional studies demonstrated positive associations.[150–157] However, only two of the eight interventional studies (an RCT[469] of aerobic and resistance exercise and a single cohort study involving Tai Chi[471]) revealed positive outcomes regarding cognition in PLWH.

McDermott and colleagues[470] conducted the only RCT to directly examine the effect of exercise on an objective measure of cognition in PLWH. Their 16-week aerobic exercise intervention, three times per week at 40-75% of heart rate reserve had no effect on Montreal Cognitive Assessment scores, nor on Trails A and B scores.[470] However, the sample size consisted of 11 participants and the Montreal Cognitive Assessment may not be sensitive to cognitive impairment in PLWH.[489] Clearly, confirmatory evidence of the effect of exercise on cognition in this population is lacking.

The Effect of Yoga on Cognitive and Physical Function

Yoga has emerged as an effective form of exercise and mindfulness-based stress reduction across many clinical populations.[677] It is an ancient practice combining postures, mindfulness, spirituality, and breath control to enhance flexibility, strength, and balance that is increasingly being recognized as a mainstream intervention to promote a more preventative and holistic health care approach.[678,679] Findings of a meta-analysis of 15 RCTs suggest that yoga interventions lasting 1-6 months are associated with enhanced overall cognitive function (Hedges' $g = 0.33$), attention and processing speed (Hedges' $g = 0.299$), executive function (Hedges' $g = 0.27$), and memory (Hedges' $g = 0.18$) in people with and without chronic diseases.[517] In fact, it appears that acute bouts of yoga may be superior to aerobic exercise for improving inhibition and working memory, as determined by a repeated-measures study of 30 healthy younger women.[680]

There are numerous mechanisms thought to underlie cognitive improvements with yoga interventions. It is possible that yoga may contribute to dominance of the parasympathetic nervous system[592,595] while down-regulating the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis.[592] A systematic review of 25 RCTs conducted with healthy and chronic disease populations revealed that those who participated in yoga improved their cortisol levels, heart rate, and blood pressure relative to controls.[590] There is also evidence that yoga and other types of mind-body exercise (including Tai Chi) are associated with improved mood; a meta-analysis of 40 interventional studies revealed that Tai Chi has positive effects on both anxiety and depression.[593] Improvements in the stress response with mind-body exercise may contribute to improved cognitive performance;[596] an RCT of 118 older adults revealed that yoga participants had an attenuated cortisol response and improved executive function relative to the control group following an 8-week yoga intervention.[596] Of note, self-reported mood stress and cortisol levels predicted executive function performance.[596] Other potential mechanisms associated with yoga interventions include the learning of novel tasks, which is associated with changes in brain structure and function,[517] sustained attention,[681] activation of the default mode network (including learning and consolidation functions),[682] and improved meta-cognition (one's conscious awareness of their cognitive processes), which is closely related to executive function.[683]

Yoga is also an effective treatment for impaired balance in people with[684–687] and without physical impairments[688,689] due to its positive effects on strength,[690] mobility,[685] balance self-efficacy,[686,687] and visuospatial memory.[691] A 2016 systematic review and meta-analysis of 6 RCTs confirmed that healthy older adults and individuals with various health conditions such as stroke, Parkinson's disease, and knee osteoarthritis reap yoga-induced benefits to postural stability and mobility.[692] The investigators suggested that health care professionals should recommend yoga to older adults as a safe and effective intervention for balance and mobility limitations.[692]

There is considerably less research evaluating the effect of yoga on balance, quality of life, and depression in PLWH. In their case-series study of three PLWH, Kietrys and colleagues (2018) observed improvements in several gait parameters (including double-limb support time, step length, stride length, stride velocity, walking velocity) and balance (as measured by the Multidirectional Reach Test) in two of the three participants following a four-week yoga intervention.[328] There is some RCT evidence for the benefits of yoga on quality of life[636] and depression[693] in PLWH; however, the former study did not involve yoga postures and the latter intervention was only a month in total duration. No RCTs to date have evaluated the impact of yoga on cognitive and physical performance among PLWH.

Purpose and Objectives

The purpose of this pilot RCT is to determine the feasibility of a yoga intervention in order to lay the groundwork for a full-scale, multi-site, community-based trial with PLWH. Specific objectives are to: **1)** Assess the feasibility of the study protocol and procedures; **2)** Compare cognitive function in PLWH in a yoga intervention group to a usual care control group among PLWH after 12 weeks of the intervention; and **3)** Compare the effects of the 12-week yoga intervention versus control on balance, walking speed, physical activity, mental health, medication adherence, and quality of life in PLWH.

Methods

Design

We propose a pilot randomized trial with two parallel groups comparing the yoga group to a usual care control group using quantitative methods of data collection. Figure 1 outlines the sequencing of the study protocol. The conceptual framework for pilot and feasibility studies created by Eldridge and colleagues[694] and the Consolidated Standards of Reporting Trials (CONSORT) 26-item checklist for randomized pilot and feasibility studies will be employed to ensure methods are properly defined and reported.[695] The study is guided by a community advisory committee comprised of seven members of the HIV community and three representatives from local HIV organizations. Our research team held consultations with the community advisory committee to assist with study design and recruitment strategy.

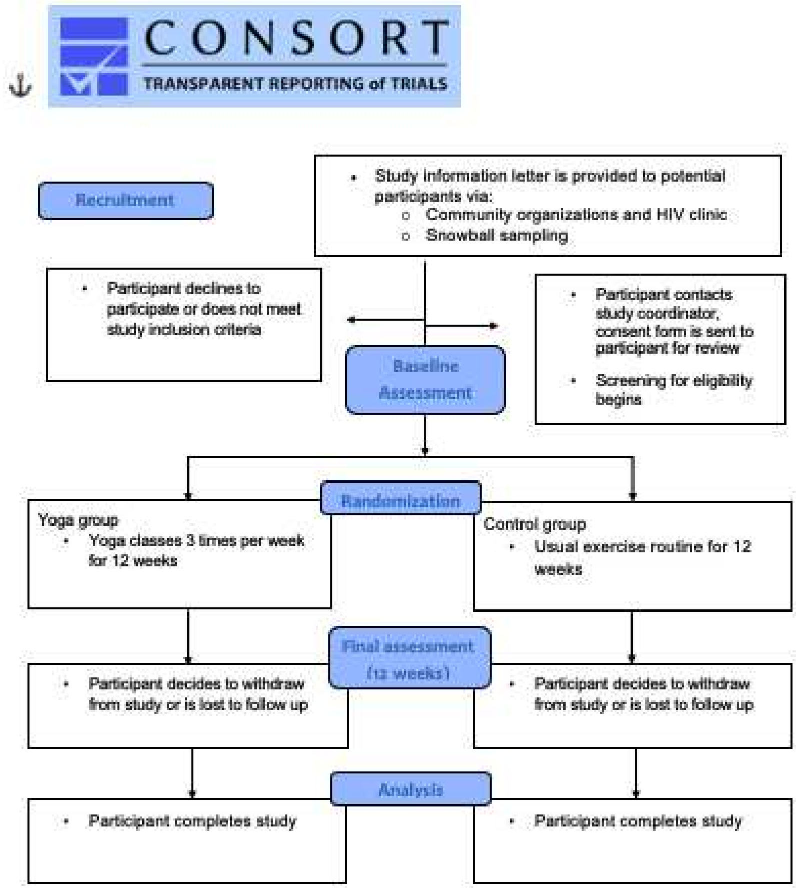

Figure 1: Consolidated standards of reporting trials flow diagram

Participants

We will include a maximum total of 25 PLWH who are aged 35 or older of any gender, identify cognitive concerns on the C3Q (Communicating Cognitive Concerns Questionnaire) with a cut-off of 35 points or less,[187] are English-speaking, live within 50 km of the study site, are able to provide informed consent, and are deemed medically stable as assessed by the Physical Activity Readiness Questionnaire Plus.[696] Study exclusion will include regular participation in a yoga program during the 6 months prior to study commencement.

Recruitment

Recruitment will occur via newsletters and posters at community organizations and health centres in Halifax, Nova Scotia. As well, staff at the local HIV Clinic have agreed to approach eligible individuals and provide them with a study information brochure. To obtain a sample that is diverse in terms of ethnicity, gender, and severity of HIV disease, we will also employ snowball sampling techniques, whereby potential participants will be asked to identify other potential participants. All interested individuals will contact the study coordinator. The coordinator will explain the general purpose and procedures of the study, risks and potential benefits, time commitment, and responsibilities of the participants. Each potential participant will be informed that health care services will not be affected by study participation or withdrawal. A copy of the consent form will be provided and reviewed and all questions answered to the potential participant's satisfaction. Potential participants who remain interested in enrolling in the study will be asked to sign the consent form approved by the local Research Ethics Board (REB).

Randomization

After baseline assessment, an individual not directly involved in the study will randomly assign participants at a 1:1 ratio to the yoga or control group using a random computer generator. Group assignment of each participant will be concealed in individual opaque envelopes that will remain sealed until after completion of the baseline assessment. The number of participants screened and randomized to each group will be recorded, as per the CONSORT extension for randomized pilot trials.[695]

Ethical Considerations

The study protocol was approved by the REB (protocol reference #1022158). The procedures will be followed in accordance with institutional ethical standards and the Helsinki Declaration. The trial was registered on clinicaltrials.gov. Proposed amendments to the protocol will be submitted for review to the REB. For ethical reasons, we cannot ask participants to avoid making medication changes; any changes participants make to their medications will be documented. Unanticipated or adverse events will be reported immediately to the REB. Participant confidentiality and autonomy will be maintained throughout the study and data will be anonymized and secured. Study data will be stored in a locked office at Dalhousie University. Electronic data will be stored in encrypted form and will exclusively be accessed by the research team. Restricting access to data on-site until the data has been appropriately coded and de-identified will mitigate the risk of residual disclosure. All data will be destroyed after seven years. Decisions to stop participating will be respected. To offset participants' personal and travel costs, we will provide bus tickets for assessments and yoga sessions, and parking reimbursement, snacks, and honoraria for the assessments.

Intervention Protocols

Yoga Group:

Groups of 4-5 participants will engage in 60-minute group-based Hatha-style yoga sessions 3 times per week for 12 weeks under the supervision of a yoga-certified physiotherapist at a local yoga studio. Classes will begin with a 15-minute warm-up, which includes seated meditation, breathing exercises, shoulder and neck stretches, back mobility exercises, and sun salutations. Then, participants will perform 10 minutes of standing and 15 minutes of balance poses, followed by 10 minutes of abdominal work and back-bends. The class will finish with five minutes of final rest (savasana). The yoga protocol can be seen in table 1.

Table 1: Yoga protocol.

Warm-up (15 minutes)	**Standing poses (10 minutes)**	**Balance poses (15 minutes)**	**Abdominals & back bends (10 minutes)**	**Cool-down (10 minutes)**
Seated meditation Alternate nostril breathing Bellows breath Shoulder/neck stretches Cat-cow Forward fold Sun salutations	Warrior 1 Warrior 2 Triangle Extended side angle Reverse warrior High lunge with twist	Tree pose Eagle pose Standing holding knee Modified warrior 3 (chair support) Half moon	Bird-dog Side plank Bridge Cobra Sphinx	Twist Cobbler's pose Hip stretches Corpse pose Side-lying Seated om

Yoga Protocol

Yoga mats, blocks, chairs, and straps will be provided to the participants. Postures will be modified for people with balance impairments or neuropathies. If participants are unable to get down to the floor or balance without support, postures will be performed with the use of a chair or other props. Since Indigenous people are over-represented in the HIV epidemic in Canada (they represented 11.3% of all new infections in 2016),[8] the sample population should reflect the cultural diversity within the catchment area of the study. Every month, a smudging ceremony with an Elder representing the Indigenous people will take place for 5-10 minutes prior to class commencement. The rationale for performing the smudging ceremony is that it is commonly associated with yoga practices;[697] in fact, a recent survey of 360 yoga practitioners identified spirituality as a common reason for starting and maintaining their yoga practice.[698]

Attendance Policy

Of the total of 36 sessions (3 classes week for 12 weeks), each participant will be encouraged to attend 70% of classes. Consideration will be given to withdrawing a participant from the study if the participant cancels or does not attend more than 6 sessions for reasons other than illness. In the event of a reversible illness that results in the participant being absent for more than 6 sessions, the participant will be withdrawn from the study and offered to be re-enrolled in the yoga group after an 8-week washout period. If a session is cancelled, a make-up session will be scheduled.

Control Group:

The control group will be asked to continue with their regular exercise routine, and to not make any changes during the study. Interested participants in the control group will be offered the opportunity to attend ongoing yoga classes as frequently as they would like following study completion.

Assessment Protocol

As per the CONSORT extension for pilot RCTs, the number of participants screened for eligibility, randomly assigned, received intended treatment, and assessed for each objective will be recorded.[695] Study data will be collected in the Physiotherapy department at Dalhousie University and managed using REDCap (Research Electronic Data Capture) software.[699] The authors will provide access to the study's REDCap data upon request. Table 2 outlines the outcome variables and measurement tools.

Table 2: Outcome variables and measurement tools

Variable	Measurement Tool	Objective measure or self-report
Yoga readiness (Previous experience with yoga, injuries, ability level)	• Yoga readiness questionnaire (yoga group only)	• Self-report
Cognitive performance	• Communicating Cognitive Concerns questionnaire (C3Q) • B-CAM (Brief Cognitive Ability Measure)	• Self-report • Objective
Motor function (balance, walking speed)	• CB&M (Community Mobility and Balance) Scale • 10-meter walk test (10MWT)	• Objective • Objective
Mental Health	• Hospital Anxiety and Depression Scale	• Self-report
Quality of Life	• Medical Outcomes Survey (MOS-HIV)	• Self-report
Medication Adherence	• Simplified Medication Adherence Questionnaire (SMAQ)	• Self-report
Physical Activity	• RAPA (Rapid Assessment of Physical Activity) • Fitbit Flex 2™ [total distance walked (km) and number of steps taken per day]	• Self-report • Objective
Participant satisfaction, safety, comfort, fatigue, benefits	• Post-participation survey (yoga group only)	• Self-report

Demographic information: We will administer a 13-item paper-based self-reported questionnaire asking about age, sex, gender, ethnicity, education level, employment, income, co-morbidities, year diagnosed with HIV, viral load (if known), CD4 count (if known), medications, comorbidities, and physical activity (how often the participant was physically active in the week prior) at baseline to describe the sample and assess group comparability. Participants randomized to the yoga group will be asked to fill out a yoga-readiness questionnaire we created to provide the yoga instructor with safety and injury information.

Primary measures: Many domains of feasibility will be assessed by both participants and study personnel using monitoring processes and a 13-item paper-based post-intervention questionnaire, which includes both questions on a Likert scale ranging from strongly disagree to strongly agree and open-ended questions (see appendix B):

1. Project coordination (team building, communication/meetings, collaboration, consensus-building, trouble-shooting, scheduling, protocol consistency, timelines). Any issues with (or changes to) the study protocol or scheduling will be documented.

2. Participant issues (recruitment, comfort, satisfaction, safety, attendance, time commitment, attrition, reasons for ineligibility drop out/declining to participate), as assessed by the post-intervention questionnaire and documentation by the study coordinator.

3. Assessment protocol elements (time and personnel requirements, usefulness of outcome variables, participant burden, feasibility) will be recorded by the study coordinator.

4. Intervention protocols (time, equipment and personnel requirements) will be recorded by the study coordinator.

5. Data quality (completeness, intra/inter-participant variability, interpretability, trends) will be checked by the study coordinator. Per the CONSORT checklist, our a priori adherence and satisfaction criteria will be met if participants attend 70% of the yoga sessions and 70% of the participants are satisfied with the yoga intervention as per the post-participation questionnaire.

Secondary and tertiary measures: Cognition, physical performance (balance, walking speed), physical activity, and affective (mental health, quality of life, medication adherence) evaluations will be administered at baseline and post-intervention (12 weeks) by a trained assessor, blinded to the group assignment. The rationale for blinding the assessor is to reduce bias in scoring during the assessment sessions. The estimated length of time for the assessment sessions is two hours per participant.

We will measure <u>cognitive function</u> using the Brief Cognitive Ability Measure (B-CAM), a computerized cognitive test developed for PLWH using Rasch measurement theory and analysis that takes 30 minutes to administer.[170,173] The B-CAM provides a measure of global cognition that is calibrated – the intervals between logits are equal, meaning the data is continuous.[173,174]

Cognitive domains tested with the B-CAM include visual detection (reaction time), Flanker task (response inhibition),[700] memory (learning and recall of 8 words), Shape 2-back (working memory),[701] Corsi block-tapping forward and back tests (visuospatial memory),[702] verbal fluency (letters F-A-S in English) mini Trail making test

B (executive function),[703] and the Tower of London test (planning).[704] The scoring of the B-CAM ranges from 0 to 24, with higher values indicating better global cognition.[174] To reduce the likelihood of practice effects, different versions of the B-CAM are performed at baseline and final assessments.[174] Group-based trajectory analysis has revealed that no practice effects were found at the item level.[174]

Self-reported cognition will also be assessed using the C3Q, an 18-item paper-based questionnaire that was developed to estimate the presence and frequency of memory, attention, executive function, visuospatial, speech and language, behaviour and emotion, and cognitive challenges among PLWH.[187] The frequency of such challenges are recorded by the participant on a three-point scale: frequently (almost every day), sometimes (once a week), or rarely (once a month).[187]

Tertiary measures: Balance will be measured using the Community Balance and Mobility (CB&M) test, a high-level balance assessment of tasks performed in the community developed for people with traumatic brain injury.[705] It is a valid and reliable measure of dynamic postural control in people with traumatic brain injury[288,705] and older community-dwelling individuals,[290] and it is not as susceptible to ceiling effects as the Berg Balance Scale.[289,290] Walking speed will be measured using the 10-meter walk test because of the association of gait speed with cognitive performance in PLWH,[93] its previous use in the HIV literature,[149] and its ability to predict survival in older adults.[271] Depression will be assessed using the Hospital Anxiety and Depression Scale (HADS), a paper-based self-report questionnaire,[445] which has very good to excellent internal consistency, test-retest reliability and convergent validity, and acceptable discriminant validity in PLWH.[441] Quality of life will be assessed using Medical Outcomes Survey for

HIV (MOS-HIV), a paper-based questionnaire which consists of 10 domains (physical function, social and role function, cognitive function, pain, mental health, energy, health distress, quality of life and overall health) with good to high internal consistency and construct validity in PLWH.[393] Physical activity will be assessed using the Rapid Assessment of Physical Activity (RAPA), a 9-item paper-based questionnaire that measures moderate and vigorous physical activity, including strength and flexibility within the last week.[373] It was validated in older adults[373] and has been used in studies with people with HIV.[375] Objective levels of physical activity (total distance walked and number of steps taken per day) will be measured using accelerometers (Fitbit flex 2™).[706] Accelerometer data will be electronically synced and downloaded after weeks 1 and 12 and stored in an encrypted file. Participants will also be asked about Medication adherence (specifically cART), measured with the paper-based Simplified Medication Adherence Questionnaire (SMAQ), which has 72% sensitivity, 91% specificity and a likelihood ratio of 7.94 for non-adherent patients.[349]

Participant Safety

Participants will be monitored throughout the yoga sessions and the assessments. If a participant presents with any medical or safety concerns, the supervising physiotherapist will provide the appropriate first aid or injury treatment, then will refer the participant to their family physician for follow-up. Any harms or unanticipated effects will be recorded as per the CONSORT checklist.[695] Due to the low-risk nature of the study, we do not anticipate any additional safety or medical issues associated with the yoga interventions.

Results

All questionnaires and measures will be assessed for missing data. The data will be analyzed to determine if the assumptions for parametric tests are met. Descriptive statistics will be used to characterize the participants. As per the CONSORT extension for pilot studies, means of all outcomes, mean change, and 95% confidence intervals will be calculated for each group separately. We will also follow the SAGER (Sex and Gender Equity in Research) guidelines[707] by disaggregating data by sex and gender. Participant dropouts will also be reported disaggregated by sex.

Data Analysis

Independent t-tests and Fisher exact tests will be used to compare the two groups at baseline. If the two groups differ at baseline, that variable will be included in the analysis as a covariate. We will analyze quantitative post-intervention questionnaire responses using Chi-square tests, and open-ended responses will be analyzed thematically. Intention-to-treat and per-protocol analyses will be used in the analysis of the secondary variables. Changes in outcome variables will be examined between groups and within groups. Floor and ceiling effects will be calculated for the CB&M. Effect sizes will be reported for each outcome. Alpha level will be set at .05 using 2-tailed for all inferences and data will be analyzed with SPSS Version 23. As this is a pilot study, sample size calculations are not recommended.[695] This pilot study will not be adequately powered to state conclusively the influence of the intervention on study outcomes but if trends are promising, a future, more adequately powered trial will be planned. This pilot study will provide preliminary data for future sample size calculations.

Anticipated Challenges and Limitations

Potential challenges will include recruitment and retention of participants over the course of the 12-week intervention. With approximately 500 PLWH living in the local area,[708] we anticipate that involving community leaders and end-users from the outset of conceptualization and planning, and conducting the study in a familiar community setting, we will successfully recruit 25 PLWH. Although attrition is of concern in exercise studies requiring multiple visits, a 2015 study on yoga and meditation reported an overall attendance rate of 89% among PLWH.[637]

Study limitations include a lack of mechanism to confirm HIV diagnoses for participants not recruited from the HIV clinic and limited study inclusion to individuals who speak and understand English which may reduce the generalizability of our findings. Participants were also not asked about substance abuse or specific comorbidities such as peripheral neuropathy, which may affect cognitive and physical performance.

Dissemination

Study results will be disseminated to PLWH, researchers, health care providers, community-based organizations, stakeholders, and policymakers. Knowledge translation will take place via peer-reviewed journals, podium and poster presentations at conferences and forums, newsletters, and presentations at community-based organizations.

Discussion

This pilot implementation trial will be the first to investigate the effect and feasibility of a yoga intervention on cognitive and physical outcomes in PLWH. Not only will the study generate preliminary data about the effects of yoga on cognitive and physical function but inform the feasibility and utility of further investigation in terms of team capacity-building, recruitment and retention strategies, and assessment of intervention protocols. The focus of the project is clearly aligned with a key research priority of the Canada-International HIV and Rehabilitation Research Collaborative (CIHRRC), which is to determine the effectiveness of rehabilitation interventions and service delivery models.[709]

Our research addresses HIV beyond a biological perspective in order to reduce not only physical limitations but also the social impact of HIV. By targeting an inexpensive non-pharmacological intervention, we hope to identify feasible community-based strategies that may contribute to slowing the health-related consequences of HIV while improving quality of life for PLWH.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Funding

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Acknowledgements

We would like to thank Dr. Jaquelin Gahagan for her contribution to the project.

Chapter 11- The Feasibility and Impact of a Yoga Intervention on Cognition, Physical Function, Physical Activity, and Affective Outcomes Among People Living with HIV: A Pilot Randomized Controlled Trial

This chapter is a manuscript that was submitted to the *Journal of the International Providers of AIDS Care (JIAPAC)* in August 2019. The article outlines the results of the randomized pilot trial and the discussion of our findings. The participants displayed impairments in physical and cognitive function at baseline. Regarding cognitive performance and self-reported cognition, 54.5% of participants scored below the mean in the Positive Brain Health Now Cohort on the B-CAM (M = 20.4, SD = 4.4), and 45.5% scored below the mean for the C3Q (M = 25.6, SD = 7.9) at baseline. In terms of physical performance, baseline comfortable and maximum gait speeds and Community Balance and Mobility scale values were below age- and sex-referenced values for all but one age group. These findings will be discussed further in Chapters 11 and 12. The correlation matrix is included in appendix D.

To cite this article:
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Contribution Statement

I developed the intervention with assistance from Dr. Marilyn MacKay-Lyons, Dr. Kelly K. O'Brien, Dr. Marie-Josée Brouillette, and Dr. Jaqueline Gahagan. My duties included being the study coordinator and a yoga instructor. I also drafted the manuscript and received edits from the co-authors.

Abstract

The purpose of this pilot randomized trial was to assess the feasibility and satisfaction of a tri-weekly 12-week yoga intervention among people living with HIV (PLWH). Other objectives included evaluating cognition, physical function, medication adherence, health-related quality of life (HRQoL), and mood among yoga participants versus usual care using blinded assessors. We recruited 22 medically-stable PLWH aged ≥35 years. *A priori* feasibility criteria were defined as ≥70% yoga session attendance and ≥70% of participants satisfied with the intervention using a post-participation questionnaire. Two participants withdrew from the yoga group. Mean yoga class attendance was 82% with 100% satisfaction. Intention-to-treat analyses (yoga n=11, control n=11) showed no within- or between-group differences in cognitive and physical function. The yoga group improved over time in HRQoL cognition (p=.047) with trends toward improvements in health transition *(p=.063)* and depression *(p=.055)*. This pilot study provides preliminary evidence of feasibility and benefits of yoga for PLWH.

Trial registration: ClinicalTrials.gov identifier: NCT03071562
https://clinicaltrials.gov/ct2/show/NCT03071562?term=NCT03071562&rank=1
Trial funding: Canadian Institutes of Health Research Catalyst Grant in HIV/AIDS Community Based Research
Keywords: HIV, AIDS, yoga, cognition, balance

What do we already know about this topic?

- Yoga is a promising intervention for improving cognition and balance among HIV-negative individuals.

How does your research contribute to the field?

- This trial was feasible and the 12-week yoga intervention provided benefits to self-reported cognition among people living with HIV.

What are your research's implications toward theory, practice, or policy?

- This study can inform clinicians and researchers about the feasibility and potential efficacy of a yoga intervention in improving self-reported cognition among people living with HIV.

Background

The most recent estimates indicate that 36.9 million people worldwide are living with HIV (Human Immunodeficiency Virus).[447] The highest percentage of people living with HIV (PLWH) is in Sub-Saharan Africa, with 53% of the global prevalence.[2] Those at risk of HIV transmission include women, men who have sex with men, transgender individuals, people who use drugs, and sex workers.[7]

Approximately 15-69% of people living with HIV (PLWH) worldwide experience some form of cognitive impairment,[47–50] which includes deficits in attention, memory, and executive function.[74,449] There are sex and gender differences in cognitive performance among PLWH, with women scoring lower on tests of attention, processing speed, executive function, and fine motor performance than men.[164] In addition to cognitive impairment, balance and gait deficits are common among PLWH[208] and are associated with elevated falls risk and mortality.[149] Some evidence has emerged to indicate that a relationship exists between physical and cognitive performance in this population.[93]

Mind-body exercise is a type of therapy such as Tai Chi and yoga that includes concentration, breathing, and body movement.[514] These interventions can have a positive effect on cognitive performance among older adults without HIV. A recent meta-analysis of 32 randomized controlled trials (RCTs) evaluated mind-body interventions (of which, 8 RCTs included a yoga intervention) and showed significant improvements in overall cognitive performance, working memory, verbal fluency, cognitive flexibility, and learning among older adults.[514] Another meta-analysis of 11 RCTs (4 RCTs with yoga interventions) conducted with older adults determined that mind-body exercise had a positive effect on overall cognition, memory, executive function, learning, and language.[515] A prominent theory explaining these cognitive benefits with yoga includes the down-regulation of the stress response and up-regulation of the parasympathetic nervous system.[592,595] No RCTs to date have evaluated the impact of a yoga intervention on cognitive performance outcomes among PLWH.

Over half of PLWH have sought complementary or alternative therapies, which include mind-body interventions such as yoga and Tai Chi.[641,710,711] Some authors have evaluated the impact of Tai Chi on health-related quality of life and mental health in this population. A single group observational study conducted with male (n = 35) and female (n = 24) PLWH reported a positive effect of Tai Chi on HIV-related psychological distress in addition to emotional, social, and overall health-related quality of life.[471] An RCT of 38 men living with AIDS (Acquired ImmunoDeficiency Syndrome) conducted by Galantino and colleagues (2005) in the United States found significant improvements in overall health-related quality of life in both aerobic exercise and Tai Chi groups versus controls.[434]

RCT and meta-analyses have also demonstrated positive effects of yoga on health-related quality of life and mood among PLWH. An RCT demonstrated significantly improvements in anxiety, depression, fatigue, well-being, and quality life in a sample of mostly female PLWH who participated in a yoga intervention compared to controls following an 8-week intervention,[712] while another RCT demonstrated positive effects on self-reported health-related quality of life and mental health among mostly female PLWH following a 12-week yoga intervention compared to controls.[636] However, the intervention did not include a physical activity component, and PLWH taking antiretrovirals were excluded from the study.[636] An RCT with a 1-month yoga intervention conducted with male (n = 24) and female (n = 20) PLWH showed a significant reduction in depression scores among yoga participants compared to controls.[693] A meta-analysis of 7 randomized studies conducted with PLWH determined that yoga interventions resulted in large improvements in perceived stress, positive affect, and anxiety compared to controls.[627] Finally, a systematic scoping review of 84 studies showed that mindfulness, relaxation techniques, cognitive-behavioral strategies, and yoga had beneficial effects on health-related quality of life and physical and psychological symptoms among PLWH.[641]

Emerging evidence also suggests that mind-body exercise can improve physical performance among PLWH. Participants in the abovementioned RCT by Galantino and colleagues (2005) who performed aerobic exercise and Tai Chi had significant improvements in balance using the functional reach test.[434] Kietrys and colleagues (2018) also observed improvements in gait and balance with their yoga intervention among two of three case-series participants.[328] Yoga has the potential to address both physical and cognitive impairments in this population. However, no RCTs to date have evaluated the feasibility and impact of yoga on cognitive and physical outcomes among PLWH.

Women are frequently under-represented in health research, particularly in HIV trials.[713] To address this gap, the SAGER (Sex and Gender Equity in Research) guidelines recommend authors report how sex (biological attributes) and gender (socially-constructed roles, behaviours, and identity) factor into the study design and present study data disaggregated by sex and gender if possible.[707] As such, we will discuss and evaluate the role of sex and gender in this study where applicable.

Purpose, Objectives, and Hypothesis

Our overall goal was to inform the design of a future, full-scale, multisite, community-based RCT to evaluate the effects of yoga on cognitive and physical function among PLWH from Halifax, Nova Scotia, Canada. Our primary objective was to assess the feasibility of a 12-week yoga intervention for PLWH in terms of participant recruitment, assessments, safety, adherence, and satisfaction with the intervention. Our secondary objective was to evaluate the effect of a 12-week yoga intervention (yoga group) versus usual care (control group) on cognitive performance and self-reported cognition among PLWH. Our tertiary objective was to compare the effects of the yoga intervention versus control on balance, walking speed, mood, medication adherence, physical activity, and health-related quality of life outcomes among PLWH. The fourth objective was to explore the relationships between cognitive performance and self-reported cognition, physical activity, and balance performance. Our hypotheses were: 1. The yoga group would experience larger improvements in cognitive performance and self-reported cognition than the control group and 2. The yoga group would experience larger improvements in physical function, health-related quality of life, and mood outcomes than the control group.

Methods

We designed a pilot RCT. The Consolidated Standards of Reporting Trials (CONSORT) checklist for pilot and feasibility studies[695] can be viewed in appendix C.

Participants

The CONSORT[714] diagram in Figure 1 shows the flow of participants through this randomized, two-parallel group, pilot trial. Participants were included in the study if they were aged 35 years or older, identified cognitive concerns on the Communicating Cognitive Concerns Questionnaire (C3Q) with a cut-off of 35 points or less at baseline,[187] lived in the Halifax Regional Municipality of Nova Scotia, Canada, were able to provide informed consent, and were medically stable as determined by the Physical Activity Readiness Questionnaire Plus.[696] PLWH already participating in regular yoga classes were excluded. We recruited participants from community and health organizations in Halifax, Canada using posters, newsletters, and clinic staff assistance. We attempted to obtain a diverse sample in terms of ethnicity and gender, therefore we also used snowball sampling techniques.

CONSORT 2010 Flow Diagram

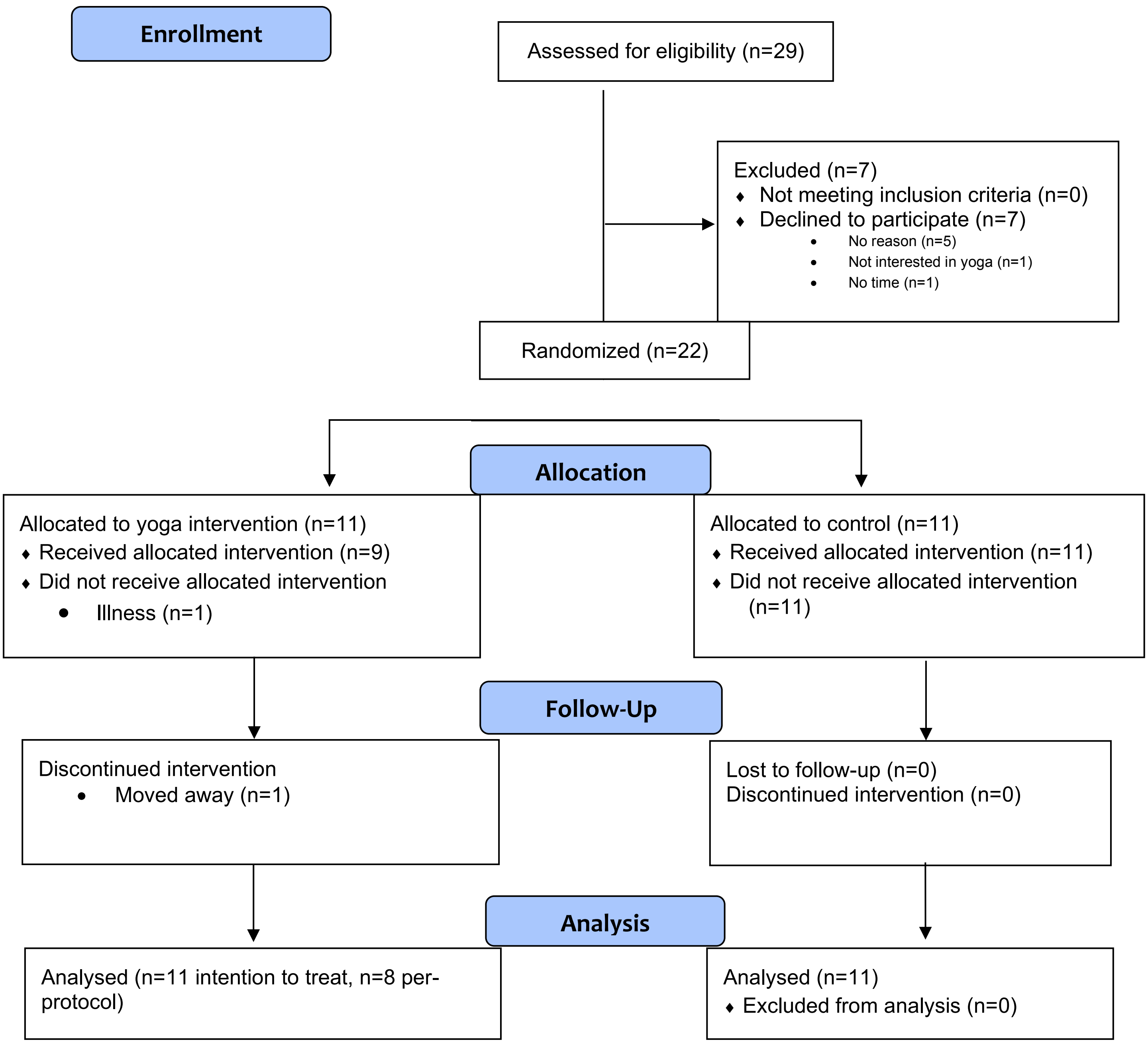

Figure 1: CONSORT flow diagram

Study procedures

We obtained ethics approval through the Nova Scotia Health Authority (protocol reference #1022158) and registered on clinicaltrials.gov (NCT03071562). Study procedures were in accordance with institutional ethical standards and the Helsinki Declaration. The study methods are described in detail elsewhere.[715] Briefly, interested individuals contacted the study coordinator who conducted a screening assessment to confirm eligibility, explained the study's purpose, procedures, risks and benefits, and time responsibilities of the study, reviewed the consent form, and answered questions. Potential participants who remained interested in the study then signed the consent form and underwent the baseline assessment, after which they were randomly assigned in a 1:1 ratio to the yoga or control group. Group assignment was determined by a random computer generator and was concealed in individual, opaque envelopes by a person unaffiliated with the study. The study coordinator opened the envelopes after completion of the baseline assessment. Blinded assessors conducted the post-intervention assessment 12 weeks later. We instructed participants to avoid revealing their group allocation to assessors. To determine the effectiveness of the blinding process, we asked blinded assessors at study completion if they knew the group assignment of each participant, and if not, their 'guess' of the assignment.

Intervention Protocols

Participants in the yoga group engaged in group-based Hatha yoga classes for 60 minutes, 3 times weekly for 12 weeks at a yoga studio. The yoga program incorporated common components of yoga: asanas (physical poses), meditation (dhyana), breathing exercises (pranayama), the study of introspection or self-study (swadhyaya), and spiritual discourse (satsang).[716] Classes began with 15 minutes of seated meditation, breathing exercises, shoulder, neck and back stretches, and sun salutations (either in seated or standing). This was followed by 10 minutes of standing poses, 15 minutes of balance poses, and 10 minutes of abdominal and back-bend poses. All classes finished with 10 minutes of cool-down stretches and final rest (savasana). Classes were adapted to all ability levels. At the yoga classes, participants were provided with yoga mats, chairs, bolsters, blocks, straps, and blankets. To honour the Mi'kmaq peoples, on whose ancestral land the classes were conducted, an Indigenous Elder performed brief monthly smudging ceremonies (the burning of plants such as sage or sweetgrass for purification[717]) prior to class commencement. Participants were not explicitly encouraged to practice at home. We directed control participants to maintain their usual physical activity levels during the study.

Participants were given $50 honoraria at baseline and final assessments. We offered bus tickets and parking reimbursement for assessments and bus tickets for those attending the yoga classes. We provided child-care reimbursement to those in the yoga group to address participation barriers, which are prevalent among female participants.[663]

Outcome Measures

We assessed the feasibility of the trial by measuring participant recruitment, assessments, safety, adherence, and satisfaction with the intervention. Participant recruitment measures (including reasons for not participating and recruitment time), assessment duration, adverse events, and adherence (number of yoga classes attended) were recorded. An *a priori* target for adherence to determine whether to proceed with a large-scale RCT was that participants attend at least 70% of the yoga classes. The post-participation satisfaction questionnaire consisted of 7 Likert scale questions ranging from strongly disagree (1) to strongly agree (5) and 6 open-ended questions. The *a priori* goal for participant satisfaction was that a minimum of 70% of participants would indicate they were satisfied with the intervention, as determined by achieving scores of ≥4 on the Likert scale for each item on the post-participation questionnaire. The questionnaire was administered to yoga participants at study completion.

Study assessments included a demographic questionnaire administered at baseline (age, gender, ethnicity, education, employment, CD4+ cell count, viral load, time since HIV diagnosis, number of comorbidities, and antiretroviral use). We administered the following paper-based self-reported questionnaires and performance-based measures at baseline and 12 weeks: the Brief Cognitive Ability Measure (B-CAM),[170,173] a computerized measure of cognitive performance with higher scores reflecting better cognitive ability; the Communicating Cognitive Concerns Questionnaire (C3Q),[187] an HIV-specific self-reported cognitive questionnaire with higher scores indicating fewer cognitive difficulties; Community Balance and Mobility Scale (CB&M),[705] a measure of dynamic balance performance where higher scores indicate better balance performance; the 10-metre walk test, an objective test of comfortable and fast gait speed;[271] the Rapid Assessment of Physical Activity (RAPA) questionnaire, a two-part, self-reported questionnaire where RAPA 1 indicates aerobic physical activity levels and the RAPA 2 indicates resistance and flexibility activities;[373] accelerometer data (Fitbit™) including steps per day and number of kilometers walked;[706] the Simplified Medication Adherence Questionnaire (SMAQ), a self-reported antiretroviral medication adherence measure;[349] the Medical Outcomes Survey-HIV (MOS-HIV) a self-reported health-related quality of life questionnaire developed for PLWH with 11 subscales (physical function, social function, role function, cognitive function, pain, mental health, energy, health distress, quality of life, general health, and health transition);[393] and the Hospital Anxiety and Depression Scale (HADS-A and -D), a self-reported mental health questionnaire.[445]

Data Collection and Analysis

Study data were collected at Dalhousie University in Halifax, Nova Scotia, and were recorded using Research Electronic Data Capture (REDCap) software.[699] The authors will provide access to the data if requested. All outcomes were assessed for missing data. Results were analysed and reported by gender, as recommended by the SAGER guidelines.[707] Although sample size calculations are not recommended for pilot studies,[695] we targeted a sample size of 25 participants in total in order to inform future sample size calculations.

Primary Outcomes

We analyzed Likert post-intervention questionnaire responses descriptively, and open-ended responses using inductive thematic analysis.[718]

Descriptive Statistics

Means, mean change, and 95% confidence intervals were calculated separately for each group as per the CONSORT guidelines.[695] Floor and ceiling effects were assessed and calculated for the CB&M by taking the proportion of the sample that scored the minimum or maximum scores.

Secondary and Tertiary Outcomes

We used intention to treat and per-protocol approaches for our secondary and tertiary outcome analyses. Spearman correlation coefficients were used to evaluate the relationship between outcomes with 0.1-0.3 representing a weak associations, 0.4-0.6 representing moderate correlations, and 0.7-0.9 representing strong associations.[719] We performed independent t-tests, Chi square, or Fisher's exact tests on demographic variables and baseline dependent measures, as appropriate.

We evaluated the data to determine whether they met the assumptions for parametric tests. If the assumptions for parametric tests were not met, we used non-parametric tests or bootstrapping. Bootstrapping is a non-parametric approach to hypothesis testing that is recommended for small samples that do not meet the assumption of normality.[720,721] This process generates an estimate of the sampling distribution of a statistic (such as the standard error or confidence interval) by performing repeated random re-sampling from the available data and estimating bias-corrected and accelerated coefficients and p-values.[720,721] We then analyzed secondary and tertiary outcomes using univariate analysis of covariance (ANCOVA) with bootstrapped confidence intervals, mixed ANCOVA, or Wilcoxon Signed Rank tests. Two-sided tests with a minimum alpha level of .05 were used for all analyses using SPSS Version 25 (IBM, 2017).[722] We calculated effect sizes using partial eta squared for parametric and r for non-parametric tests with 0.1 representing a small effect, 0.3 considered a moderate effect, and 0.5 representing a large effect.[723–725] We also conducted a separate analysis with gender as a covariate to determine its effect on all secondary and tertiary outcomes.

Supplementary Analyses (Quaternary Objective)

We performed a moderator analysis to determine the effect of the interaction between baseline cognitive and balance performance on cognitive performance at study completion.

Results

Sample Characteristics

The characteristics of the sample are summarized in Table 1.

Table 1: Characteristics of the sample at baseline (n=22 participants)

Characteristic	**Total sample (n=22)**	**Yoga condition (n=11)**	**Control condition (n=11)**	**P-value (baseline differences)**
Demographic characteristics				
Age (years), (mean, SD)	55.5 (10.7)	50.7 (10.2)	60.2 (9.2)	.034*
Gender, n (%)				.301
Male	15 (68%)	9 (82%)	6 (55%)	
Female	5 (23%)	1 (9%)	4 (36%)	
Two-spirited	2 (9%)	1 (9%)	1 (9%)	
Transgender	0 (0%)	0 (0%)	0 (0%)	
Ethnicity, n (%)				.310
Caucasian	16 (73%)	9 (82%)	7 (64%)	
Indigenous	3 (14%)	2 (18%)	1 (9%)	
Mixed ethnicity	2 (9%)	0	2 (18%)	
Black	1 (5%)	0	1 (9%)	
Education, n (%)				.411
Some high school	3 (14%)	1 (9%)	2 (18%)	
High school diploma	10 (45%)	4 (36%)	6 (55%)	
Some university	2 (9%)	2 (18%)	0	
University degree	7 (32%)	4 (36%)	3 (27%)	
Employment, n (%)				.372
Unable to work or looking for work	10 (45%)	5 (45%)	5 (45%)	
Retired or student	5 (23%)	1 (9%)	4 (36%)	
Employed for wages full-time	3 (14%)	2 (18%)	1 (9%)	
Employed for wages part-time	4 (18%)	3 (27%)	1 (9%)	
Disease-related characteristics				
CD4+ (cells/mm3) (mean, SD)	515.5 (231.4)	552.9 (184.5)	482.2 (273.2)	.547
Number of other health conditions (mean, SD)	2.09 (2.49)	2.09 (3.02)	2.09 (1.97)	1.000
Years living with HIV (mean, SD)	20.2 (13.0)	15.1 (12.1)	25.3 (12.3)	.064
Viral load, n (%)				1.000
Undetectable	16 (84%)	8 (89%)	8 (80%)	
Detectable	3 (16%)	1 (11%)	2 (20%)	
Taking antiretrovirals, n (%)				1.000
Yes	19 (86%)	10 (91%)	9 (82%)	
No	3 (14%)	1 (11%)	2 (18%)	

*Significant difference ($p < .05$). Undetectable viral load is defined as <50 copies of HIV per milliliter of blood. SD, standard deviation

Participants were on average 55.5 years old (SD = 10.7) and had been living with HIV for a mean of 20.1 years (SD = 13.0). Most participants (86%) were taking antiretrovirals, were virologically suppressed (84%), and were not immunocompromised, with a mean CD4+ count of 515.5 (SD = 231.4). Participants mostly identified as male

(68%) and Caucasian (73%), with some education (59% had some high school education or a high school diploma), and not currently working (68% were not working, retired, or studying). The two groups differed at baseline in cognitive performance (B-CAM) and age, therefore these variables were included as covariates to all parametric analyses to control for group imbalances.

Feasibility Outcomes (Primary Objective)

We approached 29 individuals to participate in the study. All were eligible and 22 (76%) agreed to participate over a 23-month recruitment period. Five individuals gave no reason for declining to participate, one person did not wish to practice yoga, and one individual reported a lack of time. We did not achieve our initial goal to reach 25 participants, as recruitment slowed during the summer months and Halifax is a small community. The blinded assessors reported that they were unaware of group allocation of any participant at follow up.

Assessments took less than 2 hours to complete and study assessors deemed them to be feasible. One minor musculoskeletal injury occurred as a result of the balance assessment. There were no known injuries associated with the yoga intervention. Two participants (9%) withdrew from the yoga group. Reasons for drop out included illness and relocating out of province. None of the participants withdrew from the control group. Mean attendance to total yoga classes was 82% (mean attendance = 29.4/36 classes), and 89% (8/9) of participants in the yoga group met the *a priori* adherence criterion. One participant was unable to attend some classes at the yoga studio; therefore, the participant was offered taped or live virtual classes, which the participant accepted.

Nine participants had difficulties syncing their accelerometers as many did not have access to smartphones or computers. As a result, the study coordinator met with participants to sync with a study computer.

Quantitative Satisfaction Questionnaire Responses

Of the 9 participants in the yoga group, 100% enjoyed the sessions, 100% felt there was some benefit from participating in yoga, 100% felt safe during the sessions, and 100% agreed or strongly agreed that they felt comfortable during the yoga sessions.

Qualitative Satisfaction Questionnaire Responses

Five themes regarding benefits of the yoga intervention emerged from the open-ended post-participation questionnaire responses: cognitive function, mood, sleep, quality of life, and social interaction. Improved thinking was identified by six participants; one participant said, "[I'm] remembering pills, … remembering to pick stuff up at the store". Five of nine participants in the yoga group reported stress relief or decreased depression as a benefit to the intervention. One participant said, "Doing the yoga sessions gave me new skills to deal with every day stresses and participating gave me something to look forward to weekly… I appreciate this study because it was something that had immediate results. It was something for 'me' and right from the beginning, it felt less of a research project and more of a therapy course." Four participants identified improved quality of life, with two specifically reporting enhanced energy as a result of the intervention. Three participants identified social interaction as a benefit of yoga as exemplified by a participant who said, "[I've] noticed that my behavior and attitude toward others has improved by the help of yoga". Others identified enhanced sleep as a result of the intervention. A participant noted, "I would sleep 4-5 hours before the yoga classes, now I can sleep 7-8 hours after the classes". One participant noted that the virtual classes were helpful, "[The] instructor was fantastic about accommodating my schedule. However, I just wish I could have attended more classes".

Descriptive Statistics

There was no missing data for secondary, tertiary, or quaternary outcomes. B-CAM, comfortable and fast gait speed, and MOS-HIV general health, mental health, and energy subscales met the assumptions for parametric tests while the other outcomes did not. Mean B-CAM scores in the overall sample at baseline were 19.0±4.6 and 19.6±5.3 at study completion. The mean C3Q scores of the overall sample were 24.6±8.1 at baseline and 25.7±6.5 at 12 weeks.

Mean overall CB&M scores were 67.1±22.3 at baseline and 68.7±22.5 at 12 weeks. The mean score on the CB&M in the overall sample (including baseline and final scores) was 67.9 (±21.1, range = 22-96). One participant (2.38% out of 42 observations) obtained a maximum score of 96 on the CB&M, and none of the participants obtained the minimum score of 0.

Effect of the Intervention

Results of the intention-to-treat analyses (n=22) are reported. When we re-analyzed the data using per protocol analyses, we found no differences in the results unless otherwise stated. We found no significant effect of gender between groups on all outcomes.

Cognitive Performance (Secondary Objective)

A summary of results for cognitive performance is shown in Table 2. There were no significant between-group effects of the yoga intervention on the B-CAM scores at study completion *[F (1, 16) = .687, CI (-1.164, 5.718) p = .353].* There were also no within-group differences on the B-CAM scores over time, as determined by the mixed ANCOVA *[F (1, 17) = 1.769, CI (-2.979, .746), p = .201].* Self-reported cognition (C3Q) scores did not differ significantly between the groups at study completion *[F (1, 16) = .002, CI (-8.362, 8.563), p = .965*]. There were also no significant within-group differences in C3Q scores (*yoga group Z = -.983, p = .326; control group Z = -.089, p = .929).*

Table 2: Cognitive outcomes

Outcome	Yoga baseline mean (SD)	Yoga post mean (SD)	Yoga mean change (SD)	Control baseline (SD)	Control post (SD)	Control mean change (SD)	95% confidence interval	P value (within groups)	P value (between groups)	Gender analysis (p-value)	Effect size
B-CAM	22.07 (3.51)	22.27 (4.38)	0.36 (3.55)	16.26 (3.53)	18.22 (5.69)	1.97 (4.29)	[*-1.164, 5.718*]†	.201	.353†	.325	Between: $\eta p^2 = .041$ Within: $\eta p^2 = .094$
C3Q	26.09 (8.03)	28.11 (5.49)	1.78 (5.14)	23.18 (8.36)	25.45 (7.24)	2.27 (11.19)	[*-8.362, 8.563*]†	.375 (yoga) .948 (control)	.965†	.760	Between: $\eta p^2 = .000$ Within: r = -.22 (yoga); -.019 (control)

†Bootstrap values are bias corrected and accelerated based on 1000 bootstrap replications. Effect sizes are partial eta squared (ηp^2) values between groups and partial eta squared (ηp^2) or r within groups. B-CAM, Brief Cognitive Ability Measure; C3Q, Communicating Cognitive Concerns Questionnaire.

Tertiary Outcomes

Physical Performance and Physical Activity Outcomes

Physical performance and physical activity results are shown in Table 3. There were no significant within- or between-group differences in balance or gait speed. We did not observe between-group or within-group differences in physical activity as measured by the RAPA and accelerometer data.

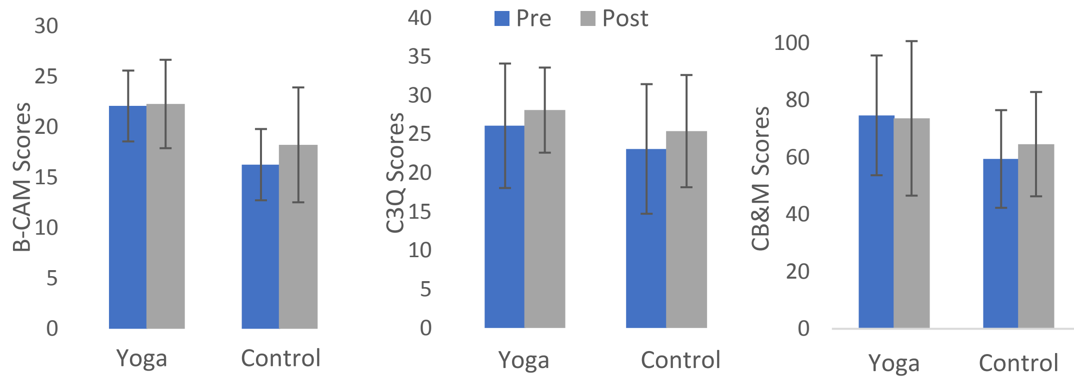

Figure 2: B-CAM, C3Q, and CB&M scores pre- and post-intervention.
B-CAM, Brief Cognitive Ability Measure; C3Q, Communicating Cognitive Concerns Questionnaire; CB&M, Community Balance and Mobility Scale

Table 3: Physical performance and activity levels

Outcome	Yoga baseline mean (SD)	Yoga post mean (SD)	Yoga mean change (SD)	Control baseline (SD)	Control post (SD)	Control mean change (SD)	95% confidence interval	P value (within groups)	P value (between groups)	Gender analysis (p-value)	Effect size
CB&M	74.73 (20.97)	73.67 (27.05)	-1.22 (7.46)	59.45 (17.15)	64.64 (18.26)	5.18 (9.91)	[-2.011, 36.723]†	.578 (yoga) .085 (control)	.107†	.533	Between: ηp² = .211 Within: r = -.151 (yoga); -.371 (control)
Comfortable gait speed	1.29 (0.29)	1.32 (0.36)	0.06 (0.13)	1.11 (.26)	1.20 (0.35)	0.09 (0.17)	[-.279, .481]	.876	.581	.338	Between: ηp² = .019 Within: ηp² = .002
Fast gait speed	1.79 (0.40)	1.73 (0.48)	-0.05 (0.15)	1.59 (0.35)	1.70 (0.43)	0.10 (0.30)	[-.221, .725]	.919	.276	.291	Between: ηp² = .074 Within: ηp² = .001
RAPA 1	4.40 (1.58)	5.33 (1.58)	0.78 (2.33)	5.09 (1.64)	5.27 (1.68)	0.18 (1.72)	[-2.716, .797]†	.563 (yoga) .594 (control)	.351†	.425	Between: ηp² = .046 Within: r = .192 (yoga) r = .150 (control)
RAPA 2	1.20 (1.32)	2.44 (0.53)	1.11 (1.62)	1.09 (1.38)	1.09 (1.30)	.00 (0.77)	[-1.892, .505]†	.125 (yoga) 1.00 (control)	.233†	.422	Between: ηp² = .095 Within: r = .42 (yoga) r = .00 (control)
Steps per day	9111.61 (4147.03)	8765.60 (4697.48)	-24.06 (1836.09)	6955.52 (4937.79)	6155.56 (3900.02)	-699.96 (2221.30)	[-1610.19, 4074.68]†	1.00 (yoga) .374 (control)	.431†	.957	Between: ηp² = .023 Within: r = .014 (yoga) r = .19 (control)
Kilometers per day	6.38 (2.56)	6.03 (2.99)	-0.05 (1.45)	4.83 (3.45)	4.33 (2.62)	-0.50 (1.63)	[-2.837, 2.887]†	1.00 (yoga) .374 (control)	.834†	.834	Between: ηp² = .002 Within: r = .014 (yoga) r = .19 (control)

†Bootstrap values are bias corrected and accelerated based on 1000 bootstrap replications. Effect sizes are partial eta squared (ηp²) values between groups and partial eta squared (ηp²) or r within groups. CB&M, Community Balance and Mobility Scale; RAPA, Rapid Assessment of Physical Activity.

Health-Related Quality of Life, Mental Health, and Antiretroviral Adherence Outcomes

Health-related quality of life and mental health results are displayed in Table 4.

There were significant within-group differences on the MOS-HIV cognitive subscale in the yoga group *(Z = -2.120, p = .047)* only. We also observed within-group difference trends among yoga participants on the MOS-HIV health transition *(p = .063)* and the HADS-depression *(p = .055)* subscales. In contrast with the intention-to-treat analyses, per protocol analyses showed a trend in improved cognitive subscale scores *(p = .094)* and no trend in improved health transition scores among yoga participants *(p = 0.125)*. We did not observe between-group differences on any other MOS-HIV subscales or the HADS questionnaire. There was no effect of the intervention on antiretroviral adherence at study completion using the SMAQ *(Chi-square = 1.650, p = .362)*.

Table 4: Health-related quality of life and mental health outcomes

Outcome	Yoga baseline mean (SD)	Yoga post mean (SD)	Yoga mean change (SD)	Control baseline (SD)	Control post (SD)	Control mean change (SD)	95% confidence interval	P value (within groups)	P value (between groups)	Gender analysis (p-value)	Effect size
General Health	61.36 (32.41)	62.78 (31.63)	7.78 (14.60)	55.00 (28.90)	54.55 (30.78)	-0.45 (19.68)	[-34.055, 34.011]	.884	.999	.627	Between: ηp² = .000 Within: ηp² = .001
Physical	81.82 (25.23)	82.41 (24.10)	3.70 (13.89)	68.94 (25.30)	76.51 (17.41)	7.58 (21.56)	[-21.085, 40.728]†	.563 (yoga) .250 (control)	.545†	.799	Between: ηp² = .042 Within: r = -.19 (yoga); -.25 (control)
Role	59.09 (43.69)	66.67 (35.36)	16.67 (25.0)	77.27 (41.01)	68.18 (46.22)	-9.09 (37.54)	[-45.927, 44.243]†	.250 (yoga) .750 (control)	.890†	.621	Between: ηp² = .001 Within: r = -.41 (yoga); -.17 (control)
Social	92.73 (13.48)	95.56 (8.82)	4.44 (19.44)	80.0 (28.28)	78.18 (24.42)	-1.82 (27.50)	[.-32.297, 10.736]†	.750 (yoga) 1.00 (control)	.536†	.326	Between: ηp² = .019 Within: r = -.17 (yoga); -.003 (control)
Cognitive	70.00 (19.11)	78.89 (17.82)	10.56 (12.86)	75.45 (14.57)	84.09 (17.44)	8.63 (18.18)	[-19.927, 36.067]†	.047* (yoga) .191 (control)	.475†	.923	Between: ηp² = .046 Within: r = -.52 (yoga); -.296 (control)
Pain	76.77 (19.53)	(72.84 (23.64)	-3.70 (20.03)	60.61 (25.03)	53.54 (28.90)	-7.07 (17.41)	[-47.781, 10.821]†	.813 (yoga) .305 (control)	.323†	.570	Between: ηp² = .089 Within: r = -.10 (yoga); -.26 (control)
Mental	74.91 (17.63)	80.00 (17.78)	6.67 (13.71)	77.82 (17.38)	70.18 (19.46)	-7.63 (16.82)	[-30.372, 6.786]	.112	.197	.980	Between: ηp² = .102 Within: ηp² = .150
Energy	64.09 (16.86)	69.44 (17.756)	8.33 (12.50)	61.36 (19.25)	56.36 (24.71)	-5.0 (18.30)	[-31.122, 17.215]	.205	.550	.555	Between: ηp² = .023 Within: ηp² =.098
Health Distress	79.55 (21.27)	69.44 (24.30)	6.67 (19.20)	80.91 (17.00)	70.45 (29.19)	-1.82 (25.52)	[-24.460, 20.790]†	.313 (yoga) .977 (control)	.719†	.399	Between: ηp² =.005 Within: r = -.27 (yoga); -.01 (control)
Quality of life	75.0 (22.36)	77.78 (19.54)	8.33 (12.50)	70.45 (21.85)	68.18 (19.66)	-2.27 (26.11)	[-27.696, 17.203]†	.250 (yoga) .625 (control)	.535†	.792	Between: ηp² = .020 Within: r = -.41 (yoga); -.09 (control)
Health Transition	56.82 (19.66)	69.44 (26.41)	19.44 (20.83)	56.82 (22.61)	70.45 (29.19)	13.63 (30.34)	[-33.667 50.265	.063^ (yoga) .176 (control)	.714†	.681	Between: ηp² = .013 Within: r = -.49 (yoga); -.31 (control)
HADS-A	6.91 (4.16)	6.00 (3.35)	-1.33 (2.69)	7.09 (4.01)	5.36 (2.66)	-1.73 (3.47)	[-3.776- 3.329]†	.180 (yoga) .219 (control)	.893†	.678	Between: ηp² = .000 Within: r = -.360 (yoga); -.285 (control)
HADS-D	3.27 (3.19)	2.11 (1.61)	-1.44 (2.24)	5.27 (4.00)	4.27 (3.92)	-1.0 (3.46)	[-1.460, 7.522]†	.055^ (yoga) .363 (control)	.147†	.272	Between: ηp² = .149 Within: r = -.475 (yoga); -.211 (control)

†Bootstrap values are bias corrected and accelerated based on 1000 bootstrap replications. Effect sizes are partial eta squared (ηp²) values between groups and partial eta squared (ηp²) or r within groups. * $p < 0.05$. ^ $p < 0.10$ (trend).

Supplementary Analyses (Quaternary Objective)

Associations with Cognitive Performance

We created a correlation matrix to determine the relationship between self-reported cognition (C3Q) and cognitive performance (B-CAM) scores, revealing that baseline C3Q was not associated with B-CAM scores at baseline *[r = .262, p = .239]*. At study completion, however, C3Q was significantly moderately associated with B-CAM scores *[r = .585, p = .007]*. Baseline balance (CB&M) scores were strongly associated with cognitive performance (B-CAM) scores at baseline *[r = .843, p = .000]* and final balance scores were associated with post-intervention B-CAM scores *[r = .612, p = .004]*. Physical activity was also related to cognitive performance in this sample. The number of steps at baseline was related cognitive performance (B-CAM) at baseline *[r = .685, p = .000]* and study completion *[r = .534, p = .015]*. Furthermore, baseline kilometers walked per day was associated with both baseline *[r = .660, p =.001]* and final B-CAM scores *[r = .504, p = .023]*.

Moderator Analysis

We found a significant interaction between CB&M and B-CAM scores at baseline in the prediction of B-CAM scores at follow up in the yoga group [*B* -0.49*,* CI (-.089, -.009), p = 0.026] but not the control group [*B* 0.002, CI (-.046, .050), *p* = 0.914].

Discussion

Feasibility

This RCT was the first to evaluate the feasibility and impact of a 12-week yoga intervention on cognitive and physical outcomes among a sample of PLWH. The intervention was feasible as determined by reasonable assessment times, lack of known adverse events, adherence to the intervention, low attrition, and participant satisfaction. No known injuries occurred as a result of the yoga intervention, providing evidence that this is a safe form of exercise for PLWH. Furthermore, the participants reported 100% satisfaction and comfort with the intervention. Although we did not achieve the anticipated sample size within the time frame to conduct the study, we met the *a priori* targets for adherence and satisfaction, which indicate that a future large-scale RCT should be conducted. In order to meet recruitment targets, future RCTs evaluating cognitive and physical performance outcomes among PLWH should use multiple sites. Our findings can inform future power calculations for large scale RCTs evaluating cognitive and physical outcomes among PLWH.

The rates of attrition (less than 10%) and adherence to the yoga classes (82%) in this study are encouraging and are likely due to high participant satisfaction. Three meta-analyses[323,601,726] and one systematic scoping review[641] have identified high levels of withdrawal from exercise trials (20-29%) and mind-body interventions (39%), as well as variable adherence (61-100%) among PLWH to these interventions. Another study evaluated the feasibility of a yoga intervention for PLWH and observed similar feasibility outcomes to our study, reporting an average of 88% attendance to the classes and 83% retention at study completion.[637] However, retention in the control group was poor (50%) in the aforementioned study and the authors posited that this could be attributed to a lack of meaningful intervention.[637] In comparison, we had 100% retention in our control group at study completion, likely due to the short study duration and small time commitment.

Cognitive Performance

We found no significant improvement in cognitive performance following the 12-week yoga intervention. This finding is in keeping with those of McDermott et al. (2017), whose 16-week aerobic exercise intervention (n=11) did not have an effect on cognitive performance among PLWH.[470] Evidence from the cross-sectional literature has showed positive associations between physical activity and better cognitive function among PLWH,[150–157] but RCT evidence has yet to determine a causal relationship. There are a few potential reasons for the lack of effect of the intervention on cognitive performance in the present study. Firstly, the small sample size was not sufficient to detect a change in outcomes. Secondly, there may have been some factors related to the dose of the intervention. For example, results from a meta-analysis of exercise moderators among older healthy adults indicates that more frequent (5-7 sessions per week) exercise sessions have larger benefits for cognitive performance than less frequent sessions (3-4 per week).[511] The intervention may also have been too short in total duration, as evidenced by a systematic review that determined that total exercise duration was the most potent predictor of cognitive performance and the authors recommended that exercise interventions for older adults last at least 52 hours in total.[600] Finally, the impact of social engagement on cognitive performance should be investigated further in the HIV population. Fazeli and colleagues (2014) performed a cross-sectional analysis and concluded that the combination of physical activity with social interaction and employment had a stronger impact on cognitive performance than each of these factors alone.[150] Future large-scale RCTs evaluating cognitive outcomes among PLWH should involve longer exercise interventions and active control groups.

Self-Reported Cognition

Despite the lack of improvement in objective cognitive performance in this sample, there were significant improvements over time on the cognitive subscale of the MOS-HIV among yoga participants. This finding is surprising, as we did not observe concurrent improvements in self-reported cognition in the yoga group when measured using the C3Q. Both questionnaires have items measuring self-reported executive function, attention/concentration, and memory but the items on the C3Q are more specific than those in the cognitive subscale of the MOS-HIV, and the C3Q also includes items on language and motivation.[187] Self-reported cognition is an important clinical outcome in this population. As such, more research is needed to determine a gold-standard measure of self-reported cognition among PLWH.

We observed significant improvements over time among yoga participants on the MOS-HIV cognitive subscale with an intention-to-treat analysis but no improvement when using a per-protocol analysis. This is an unexpected result as intention-to-treat analyses are more conservative.[727] Our results may be explained by a participant in the yoga group who did not achieve the 70% adherence target but had improvements in self-reported cognition.

Health-Related Quality of Life and Mental Health

There were trends toward improvements in the MOS-HIV health transition subscale and depression as measured using the HADS among yoga participants. We also found qualitative reports of improved social interaction among yoga participants. This evidence is in keeping with other literature evaluating the effect of mind-body interventions on health-related quality of life outcomes among PLWH. An observational study of male and female PLWH determined that Tai Chi benefited cognitive health-related quality of life as measured by the FAHI (Functional Assessment of HIV Infection).[471] Another study found a positive effect of a yogic breathing and meditation intervention on the general health, social function, and cognitive function subscales of the MOS-HIV among PLWH.[728] Galantino and colleagues (1997) observed within-group differences in their aerobic exercise and Tai Chi groups on health transition scores of the MOS-HIV, with no corresponding changes in the control group among men with AIDS.[474] Similarly, a pilot RCT determined that a meditation intervention enhanced health-related quality of life in a sample of mostly male PLWH.[729] In contrast, Agarwal et al. (2015) did not find an effect of yoga on health-related quality of life among mostly male PLWH as measured using the Short Form-36.[637] However, the demographics between that study were different than the present study as their inclusion criteria were PLWH who used crack cocaine.

Physical Performance

There is some RCT evidence to indicate that yoga can improve balance among older adults without HIV.[684–687] In fact, it appears that yoga is as effective as Tai Chi and balance training at improving balance performance among older fallers.[730] However, in the present study, we found no effect of yoga on dynamic balance. This lack of effect may be related to the variation in balance performance observed among some participants in the control group and the small sample size. No studies have evaluated CB&M performance among PLWH, but baseline values in this study were lower than normative values for healthy adults in all age categories except one (ages 60-69).[322] To date, no balance measures have been validated with PLWH. Further research in this area is needed to investigate balance impairments and appropriate balance performance measures in this population.

Association between Cognitive and Physical Performance

The strong association between cognitive performance and balance found in this study is of interest, as this finding corroborates the results of other studies conducted with healthy older adults and individuals with mild cognitive impairment. A study conducted with older adults from South Africa showed a negative relationship between time taken to tandem walk 10 metres and the number of correct responses on the Stroop task, which is indicative of an association between physical and cognitive performance.[731] Another study conducted with healthy older adults from Malaysia determined that a positive relationship exists between dynamic balance and digit symbol test and matrix reasoning tests.[732] In the same study, an agility test predicted performance on cognitive tests such as the digit span test, clock drawing test, and the Mini Mental State Examination.[732] A study conducted with older adults with mild cognitive impairment determined that comfortable gait speed and Timed Up & Go performance were each associated with executive function performance using the Trails Making B test and the Stroop-Interference test.[733] Among individuals with subcortical dementia, a reduction in gait speed is related to changes in subcortical structures, connections between frontal and subcortical structures, and subcortical neurotransmitters.[734]

There is evidence of an association between physical and cognitive performance among PLWH as well. A large multi-site study of 1,549 mostly male PLWH and HIV-negative individuals reported that slowed gait was strongly associated with worse neuropsychological test scores.[93] Another study of 164 mostly female PLWH determined that motor impairment (as measured by the HIV Dementia Motor Scale), cognitive dysfunction, and cerebrovascular disease were related to each other at baseline.[97] The underlying pathology of this relationship is thought to include inflammation and underlying cardiovascular comorbidities.[97,735] Future work should evaluate the interaction between balance and cognitive performance among PLWH with a larger sample.

Study Limitations

There are several limitations to the present study that may have contributed to our findings. The principal investigator taught the yoga classes to the participants, which could bias the results. Recruitment was limited by the small number of PLWH in the geographical area. We also were only able to recruit 5 PLWH who identified as female. Due to the small number of female and two-spirited participants, it was not possible for us to report the results disaggregated by gender. Rather, gender was entered into the analyses for each variable as a covariate to determine if differences existed between groups. As a result, sex and gender may have had an effect on the uptake and impact of the yoga intervention. We also did not report study withdrawal by gender to avoid identifying participants. The small sample size may have negatively affected the process of randomization, as it is difficult to obtain equal groups[736] which may have had a confounding effect on outcomes. Changes in medications, substance use, and other factors could have contributed to the variation in cognitive and physical performance observed in this sample. As such, stratification based on cognitive performance at baseline may be useful for future RCTs. Finally, the use of a passive control group limited our ability to determine the effect of social interaction on cognitive and affective outcomes.

Conclusion

This 12-week yoga intervention was feasible as determined by assessment protocols, adherence to yoga sessions, small attrition rates, and participant satisfaction. Our results indicate that a future multi-site RCT is warranted. We found no significant differences in cognitive or physical performance between groups but there was a significant improvement in MOS-HIV cognitive subscale scores, and trends toward improvements in health-related quality of life subscales and depression scores in the yoga group following the intervention. Future research should follow the SAGER guidelines and employ sex and gender-based analyses in order to explore the impact of sex and gender on health outcomes among PLWH.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Chapter 12-Discussion

Reflections and Future Directions

The ultimate aim of this thesis was to determine the feasibility and potential effectiveness of a yoga intervention on cognition, physical performance, and affective outcomes among PLWH in Halifax. In order to do this, we first performed a scoping review to map the available literature on physical activity and exercise and cognitive outcomes among PLWH. The scoping review helped us to identify important gaps in the literature and to determine future areas of study. The second step was to determine which barriers and facilitators to physical activity and exercise (specifically yoga) PLWH experience using a qualitative study design. This step was crucial to the design of the pilot randomized trial, as we were able to recruit many of the same participants for both studies and we were able to address many barriers prior to trial commencement. For example, we discovered that many of the participants interviewed did not fully understand what yoga was and what exactly it entailed. To address this barrier, I provided a workshop to explain what yoga is and to demonstrate yoga poses. Other participants identified a lack of physical capability and self-efficacy to perform yoga; therefore, I showed them some modifications for different physical abilities, explained that yoga can be modified for any person, and that there is no judgement of other participants in the classes. This process helped to build participant self-efficacy prior to and during the yoga intervention, which was the third step of the project. When the yoga classes started, some participants were initially concerned about their appearance or their physical abilities, but, with encouragement, quickly became more comfortable with the intervention.

Community-based research, an approach that equitably involves all partners in the research process, was a fundamental aspect of this project. As such, we formed a Community Advisory Committee consisting of seven PLWH and three representatives from local HIV organizations which guided both the qualitative study (Chapter 9) and the implementation of the randomized pilot study (Chapters 10 and 11). We also worked closely with local and national AIDS service organizations such as Healing Our Nations, Nova Scotia AIDS Coalition, Mainline, Direction 180, Stepping Stone, and the Canadian Aboriginal AIDS Network. As a direct result of the relationships we formed with these organizations, I was asked to begin teaching yoga classes at the Nova Scotia AIDS Coalition for their members which helped to transition the intervention from a research setting to a community setting.

Reflections of Role of Gender and Ethnicity in HIV Research

My thesis addressed the role of gender and ethnicity in service provision and uptake among PLWH. I was conscious from the outset that female, transgender, and two-spirit individuals are under-represented in the available research conducted with PLWH; hence, these voices are not often heard in a research context. We purposefully attempted to recruit non-male and non-Caucasian identifying individuals to participate in the qualitative and quantitative studies. Potential female-identifying participants shared with us the challenges of participating in a yoga intervention, particularly a lack of child-care services. To address these obstacles, we offered child-care compensation for participants in the yoga group. Future studies could explore ways to engage female, transgender, and two-spirit PLWH in research and to address barriers to exercise participation.

Despite a concerted attempt to recruit non-male participants, the majority in both studies were male. It is important to note, however, that the proportion of female participants in both the studies (25% and 23%, respectively) reflected the gender demographics in HIV prevalence of Canada, with women making up 23% of PLWH.[8] Unfortunately, most of the female participants in the pilot RCT were randomized to the control group. As a result, separate analyses for each gender was not feasible and the generalizability of the findings is limited. To ensure representation of all genders in future trials, investigators should perform separate analyses for each gender and could consider using purposive sampling to obtain gender diversity in HIV samples.

We were able to forge meaningful relationships with Indigenous AIDS service organizations in the Halifax area, whose support was critical to the success of the studies. The partnership seemed to be a natural fit, in part because of the common goal of yoga and Indigenous health of seeking a balance between spiritual, emotional, physical, and mental well-being. To promote the alignment with Indigenous spiritual practices, we scheduled monthly smudging ceremonies with an Indigenous elder during yoga sessions.

Reflections on Lessons Learned

I learned many invaluable lessons over the course of my doctoral studies. I quickly learned to be flexible and adaptable to the participants' schedules. Working with participants from many different cultural and socioeconomic backgrounds meant that I had to expect the unexpected and change plans as needed. For example, many participants had no access to laptops and smartphones, which made the syncing of accelerometers difficult. On future research projects, I would employ the use of a technology expert to assist participants with accelerometers.

There was considerable variation in cognitive performance and self-reported cognition among the participants. I attribute some of this variation to changes in medications such as anti-depressants and antiretrovirals, as well as the episodic nature of HIV itself. In future work with larger-scale RCTs, I would closely monitor these medications and attempt to ensure participants are on a stable regimen as part of the inclusion criteria of the study. A surprising aspect of this study was that there were significant differences between exercise groups in terms of baseline cognitive performance and age. I attribute these differences mainly to the small number of participants in each group. For example, an older participant and a participant with lower cognitive performance at baseline skewed the data of the control group toward a higher mean age and lower cognitive performance. As a result, we had to control for group imbalances using age and baseline cognitive performance as covariates. If the study groups had been larger, randomization may have been more successful in reducing between-groups variability. Further, randomization with stratification based on cognitive performance would be possible in a fully powered study.

Implications for Future Research

PLWH live with complex multi-morbidity spanning all domains of the International Classification of Functioning, Disability and Health (ICF). In this study, we observed clinically relevant cognitive, gait speed, and balance impairments among our participants. Regarding cognitive performance, 12/22 or 54.5% of our participants at baseline ($M = 19.0$, $SD = 4.6$) scored below the mean in the Positive Brain Health Now cohort ($M = 20.4$, $SD = 4.4$) on the B-CAM. In terms of self-reported cognition, 10/22 (45.5%) of our participants ($M = 24.6$, $SD = 8.1$) scored below the mean for the Positive Brain Health Now cohort ($M = 25.6$, $SD = 7.9$) on the C3Q at baseline. Baseline comfortable and maximum gait speeds and Community Balance and Mobility values were below age- and sex-referenced values for each age group[317, 322] except for one female participant in the 60-69 age range. Despite the clear need for cognitive and physical rehabilitation for PLWH, the focus remains primarily on pharmacological management for these individuals. Yoga is becoming a mainstream non-pharmaceutical adjunct to more conventional health care interventions. Relative to drug therapy, yoga is an inexpensive form of preventative and holistic exercise that addresses multiple health domains commonly affected by HIV. As such, yoga is a promising addition to current HIV self-management. Mind-body interventions including yoga should be investigated further to determine effects on cognitive, physical, and mental health among PLWH.

The construct of self-reported cognition emerged in this study as important and worthy of further exploration in the HIV population. Self-reported cognition may represent a different construct than objective cognitive performance among PLWH[187] but both should be captured in interventional research. For the successful implementation of an intervention, researchers should look beyond the physiological and biological evidence; the participant's experience with the intervention is an essential element of study feasibility and implementation. Further exploration is needed to establish a gold standard self-reported cognition measure for use with this population.

Based on our results, a future full-scale RCT is warranted in order to further investigate the effect of yoga on cognitive and physical performance among PLWH. This RCT should include an active control group and multiple sites to fully investigate the effectiveness of yoga in this population. Investigators could consider adding a self-reported disability measure and a measure of strength and physical performance such as the 5-times-sit-to-stand test or the Short Physical Performance Battery. Additional work is needed to identify strategies to maintain the high adherence and low attrition levels that we observed in our study. As well, it would be informative to determine whether home-based or virtual exercise interventions are feasible and acceptable for participants in comparison to group-based classes.

Implications for Policy

This focus of my thesis is aligned with two goals of the Federal Initiative to Address HIV/AIDS in Canada: #2 (slow the progression of the disease and improve quality of life) and #3 (reduce the social and economic impact of HIV/AIDS). This doctoral work is also aligned with the six priorities of The Canada-UK HIV and Rehabilitation Research Collaborative (CIHRRC): HIV and the brain, disability and episodic disability, HIV and aging across the life course, concurrent health conditions, access to rehabilitation interventions and service delivery, effectiveness of rehabilitation, and improving outcome measurement in HIV and rehabilitation research.[709] We have identified potential community-based strategies aimed at slowing the health-related consequences of HIV and improving health-related quality of life. If the effectiveness of yoga-based therapy is demonstrated in larger scale studies, health care providers may employ this intervention to reduce the social and economic impact of HIV.

PLWH are susceptible to cognitive and physical impairments. In the general population, the evidence indicates that exercise interventions are effective in improving physical and cognitive function. However, it is clear that PLWH are not provided the access to timely preventative and rehabilitation services. Furthermore, only two HIV clinics (one primary care clinic and one specialist clinic) in Canada have an occupational health therapist on staff, and no clinics offer physiotherapy services.[737] There is a need to consider HIV-specific issues when providing rehabilitation services to PLWH in Canada. Therefore, PLWH with self-reported cognitive concerns should be offered formal neuropsychological testing. Routine screening for sarcopenia, osteoporosis, frailty, and balance impairments should be performed in a primary care setting as there are significant negative health consequences associated with such impairments. Finally, it is important to diversify the health management options for the people we serve. PLWH with cognitive and physical impairments should be offered physical and occupational therapy services as part of routine care to help manage the sequelae of HIV.

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RE: idre20:Exercise and cognitive function in people living with HIV: a scoping review

Academic UK Non Rightslink <permissionrequest@tandf.co.uk> Mon, Sep 9, 2019 at 11:37 AM
To: AQ <adriaquigley@gmail.com>

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Adria Quigley, PhD(c)

[Quoted text hidden]
Information Classi cation: General

AQ <adriaquigley@gmail.com> Wed, Oct 2, 2019 at 5:42 P
To: Journalpermissions@springernature.com

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I am requesting the use of a submitted manuscript "*Effects of Exercise on Cognitive Performance in Older Adults: A Narrative Review of the Evidence, Possible Mechanisms, and Recommendations for Exercise Prescription*" for inclusion in my doctoral thesis. Please see the attached letter and fill it out as soon as possible.

Thanks

--
Adria Quigley, PhD(c)
(pronouns; "she" and "her")

Journalpermissions <journalpermissions@springernature.com> Fri, Oct 4, 2019 at 8:30 AM
To: AQ <adriaquigley@gmail.com>

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To: AQ <adriaquigley@gmail.com>

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Kind regards,

Paloma

Gmail

AQ <adriaquigley@gmail.com>

RE: caic20:Using the Theoretical Domains Framework to identify barriers and facilitators to exercise among older adults living with HIV

Academic UK Non Rightslink <permissionrequest@tandf.co.uk> Wed, Sep 4, 2019 at 5:53 AM
To: Adria Quigley <adriaquigley@gmail.com>

Dear Adria Quigley,

Material Requested: 'Adria Quigley, Larry Baxter, Laura Keeler & Marilyn MacKay-Lyons (2019) Using the Theoretical Domains Framework to identify barriers and facilitators to exercise among older adults living with HIV, AIDS Care, 31:2, 163-168, DOI: 10.1080/09540121.2018.1499860'

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Gmail **AQ <adriaquigley@gmail.com>**

RE: Journal of the International Association of Providers of AIDS Care

Kathy Tooch <Kathy.Tooch@sagepub.com> Fri, Sep 27, 2019 at 6:35 PM
To: Katie Willis <Katie.Willis@sagepub.com>, "adriaquigley@gmail.com" <adriaquigley@gmail.com>, Umair Shafique <Umair.Shafique@sagepub.com>

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Thanks,

Kathy

Kathy Tooch

Contracts Project Manager and Paralegal

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Appendix B-Postparticipation Questionnaire

EXERCISE SESSIONS				
Please check the box (√) that indicates your level of agreement with each of the following statements.				
Safety: I felt safe during the exercise sessions.				
☐ Strongly disagree	☐ Disagree	☐ Neutral	☐ Agree	☐ Strongly agree
Comments:				
Fatigue: I felt fatigued by the end of each exercise session.				
☐ Strongly disagree	☐ Disagree	☐ Neutral	☐ Agree	☐ Strongly agree
Comments:				
Comfort: I felt comfortable during the exercise sessions.				
☐ Strongly disagree	☐ Disagree	☐ Neutral	☐ Agree	☐ Strongly agree
Comments:				
Progression: The difficulty of the exercise sessions over the 12-week study was increased appropriately.				
☐ Strongly disagree	☐ Disagree	☐ Neutral	☐ Agree	☐ Strongly agree
Comments:				
Enjoyment: I enjoyed the exercise sessions.				
☐ Strongly disagree	☐ Disagree	☐ Neutral	☐ Agree	☐ Strongly agree
Comments:				
Motivation: I was motivated to work hard during the exercise sessions.				
☐ Strongly disagree	☐ Disagree	☐ Neutral	☐ Agree	☐ Strongly agree
Comments:				
Benefits: In the end, I feel the exercise sessions were beneficial.				
☐ Strongly disagree	☐ Disagree	☐ Neutral	☐ Agree	☐ Strongly agree
Comments:				

GENERAL QUESTIONS ABOUT THE PROJECT
1. Have you noticed anything in your day-to-day life that you feel has been affected by participating in this project?
2. Is there anything that you feel has been particularly helpful about having participated in this project?
3. Is there anything that has been disappointing about participating in this project?
4. Have you noticed any changes in your thinking ability since participating in this project? If so, describe the change(s)?
5. Have you noticed any changes in the quality or length of your sleep since participating in this project? If so, describe the change(s)?
6. Any additional comments?

Appendix C-CONSORT 2010 Checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	176
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	176
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	179-182
	2b	Specific objectives or research questions for pilot trial	182
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	183-186
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	204
Participants	4a	Eligibility criteria for participants	183
	4b	Settings and locations where the data were collected	188
	4c	How participants were identified and consented	183-185
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Protocol; 185-186
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	186-187
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	186
Sample size	7a	Rationale for numbers in the pilot trial	188
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			

Section/Topic	Item No	Checklist item	Reported on page No
Sequence generation	8a	Method used to generate the random allocation sequence	185
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	185
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	185
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	185
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	185
	11b	If relevant, description of the similarity of interventions	Protocol; 185-186
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	188-189
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	See flow diagram, 191
	13b	For each group, losses and exclusions after randomisation, together with reasons	See flow diagram, 191
Recruitment	14a	Dates defining the periods of recruitment and follow-up	191
	14b	Why the pilot trial ended or was stopped	191
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Tables 1-4
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	See flow diagram
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Tables 2, 3, 4,
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	198

Section/Topic	Item No	Checklist item	Reported on page No
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	192
	19a	If relevant, other important unintended consequences	n/a
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	204
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	198-205
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	198-205
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	198-203
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	176
Protocol	24	Where the pilot trial protocol can be accessed, if available	184
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	176
	26	Ethical approval or approval by research review committee, confirmed with reference number	184

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendix D-Correlations

		BCAM pre	BCAM post	C3Q pre	C3Q post	HADS-A pre	HADS-A post	HADS-D pre	HADS-D post	CB&M pre	CB&:M post	Gait speed pre slow	Gait speed post slow	Gait speed pre fast	Gait speed post fast	RAPA 1 pre	RAPA 2 Pre	RAPA 1 post	RAPA 2 post	Steps/day pre	Km per day pre	Steps/day post	Km per day post	standard general health pre	standard general health post	standard physical pre	standard physical post	standard role pre	standard role post
BCAM pre	Correlation Coefficient	1.000	.692**	.262	.310	-.085	.002	-.293	-.222	.843**	.827**	.588**	.405	.655**	.396	-.329	-.019	.079	.480*	.685**	.660**	.747**	.715**	.452*	.476*	.698**	.559*	.096	.122
	Sig. (2-tailed)	.	.001	.239	.184	.707	.994	.186	.347	.000	.000	.004	.077	.001	.084	.145	.935	.739	.032	.000	.001	.000	.000	.035	.034	.000	.010	.669	.609
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
BCAM post	Correlation Coefficient	.692**	1.000	.128	.585**	.033	-.145	-.221	-.108	.703**	.612**	.529*	.380	.553*	.419	-.426	.047	.022	.461*	.534*	.504*	.472*	.450*	.260	.511*	.519*	.533*	.302	.391
	Sig. (2-tailed)	.001	.	.591	.007	.889	.541	.350	.651	.001	.004	.016	.099	.011	.066	.061	.844	.927	.041	.015	.023	.036	.047	.268	.021	.019	.016	.196	.089
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
C3Q pre	Correlation Coefficient	.262	.128	1.000	.413	-.384	-.404	-.426*	-.279	.145	.051	-.005	-.072	-.021	.012	-.125	-.108	.575**	.028	.239	.291	.073	.145	.372	.339	.463*	.145	.189	.227
	Sig. (2-tailed)	.239	.591	.	.070	.078	.077	.048	.233	.518	.829	.983	.763	.925	.960	.589	.640	.008	.906	.284	.188	.761	.541	.088	.143	.030	.543	.400	.337
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
C3Q post	Correlation Coefficient	.310	.585**	.413	1.000	-.073	-.435	-.389	-.503*	.385	.426	.463*	.317	.462*	.430	-.226	.254	.538*	.607**	.502*	.513*	.387	.458*	.260	.523*	.537*	.628**	.249	.315
	Sig. (2-tailed)	.184	.007	.070	.	.760	.055	.090	.024	.094	.061	.040	.173	.040	.059	.337	.279	.014	.005	.024	.021	.092	.042	.268	.018	.015	.003	.290	.177
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
HADS-A pre	Correlation Coefficient	-.085	.033	-.384	-.073	1.000	.769**	.624**	.144	-.304	.030	.280	.248	.201	.271	-.012	.008	-.285	.118	-.033	-.057	.037	.001	-.502*	-.237	-.278	.025	-.579**	-.386
	Sig. (2-tailed)	.707	.889	.078	.760	.	.000	.002	.545	.169	.899	.207	.291	.370	.248	.959	.973	.224	.620	.882	.800	.877	.997	.017	.314	.210	.917	.005	.093
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
HADS-A post	Correlation Coefficient	.002	-.145	-.404	-.435	.769**	1.000	.484*	.223	-.262	-.078	.132	.032	.059	.021	.150	-.180	-.271	-.040	-.068	-.087	.088	.015	-.321	-.312	-.252	-.226	-.738**	-.515*
	Sig. (2-tailed)	.994	.541	.077	.055	.000	.	.031	.345	.264	.745	.580	.894	.804	.929	.527	.446	.248	.868	.775	.717	.712	.949	.168	.181	.284	.338	.000	.020
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
HADS-D pre	Correlation Coefficient	-.293	-.221	-.426*	-.389	.624**	.484*	1.000	.719**	-.490*	-.324	-.325	-.370	-.262	-.363	-.273	-.417	-.513*	-.328	-.415	-.468*	-.248	-.284	-.704**	-.762**	-.475*	-.282	-.492*	-.631**
	Sig. (2-tailed)	.186	.350	.048	.090	.002	.031	.	.000	.020	.163	.140	.109	.238	.116	.232	.060	.021	.158	.055	.028	.292	.224	.000	.000	.025	.228	.020	.003
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
HADS-D post	Correlation Coefficient	-.222	-.108	-.279	-.503*	.144	.223	.719**	1.000	-.301	-.447*	-.463*	-.552*	-.390	-.515*	-.198	-.582**	-.563**	-.433	-.320	-.383	-.234	-.310	-.454*	-.629**	-.406	-.444*	-.059	-.337
	Sig. (2-tailed)	.347	.651	.233	.024	.545	.345	.000	.	.196	.048	.040	.012	.089	.020	.402	.007	.010	.056	.169	.096	.322	.183	.044	.003	.076	.050	.804	.146
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

		BCAM pre	BCAM post	C3Q pre	C3Q post	HADS-A pre	HADS-A post	HADS-D pre	HADS-D post	CB&;M pre	CB&;M post	Gait speed pre slow	Gait speed post slow	Gait speed pre fast	Gait speed post fast	RAPA 1 pre	RAPA 2 Pre	RAPA 1 post	RAPA 2 post	Steps/day pre	Km per day pre	Steps/day post	Km per day post	standard general health pre	standard general health post	standard physical pre	standard physical post	standard role pre	standard role post
CB&M pre	Correlation Coefficient	**.843****	**.703****	.145	.385	-.304	-.262	-.490*	-.301	1.000	**.895****	.503*	.488*	**.577****	.466*	-.339	.119	.233	.409	**.705****	**.695****	**.736****	**.737****	**.551****	**.605****	**.723****	**.734****	.372	.414
	Sig. (2-tailed)	.000	.001	.518	.094	.169	.264	.020	.196	.	.000	.017	.029	.005	.038	.133	.607	.322	.073	.000	.000	.000	.000	.008	.005	.000	.000	.089	.069
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
CB&M post	Correlation Coefficient	**.827****	**.612****	.051	.426	.030	-.078	-.324	-.447*	**.895****	1.000	**.678****	**.625****	**.745****	**.574****	-.280	.246	.249	.527*	**.750****	**.714****	**.791****	**.791****	.401	.555*	**.699****	**.794****	.101	.309
	Sig. (2-tailed)	.000	.004	.829	.061	.899	.745	.163	.048	.000	.	.001	.003	.000	.008	.232	.296	.290	.017	.000	.000	.000	.000	.080	.011	.001	.000	.670	.185
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Gait speed pre slow	Correlation Coefficient	**.588****	.529*	-.005	.463*	.280	.132	-.325	-.463*	.503*	**.678****	1.000	**.863****	**.857****	**.824****	-.023	.220	.119	**.679****	**.659****	**.616****	**.566****	.540*	.252	.514*	.318	.497*	.000	.112
	Sig. (2-tailed)	.004	.016	.983	.040	.207	.580	.140	.040	.017	.001	.	.000	.000	.000	.923	.339	.617	.001	.001	.002	.009	.014	.257	.020	.150	.026	1.000	.637
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Gait speed post slow	Correlation Coefficient	.405	.380	-.072	.317	.248	.032	-.370	-.552*	.488*	**.625****	**.863****	1.000	**.760****	**.931****	.048	.350	.145	.437	.484*	.459*	.341	.329	.188	.467*	.287	.504*	.053	.243
	Sig. (2-tailed)	.077	.099	.763	.173	.291	.894	.109	.012	.029	.003	.000	.	.000	.000	.842	.130	.543	.054	.031	.042	.141	.156	.428	.038	.220	.023	.826	.302
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Gait speed pre fast	Correlation Coefficient	**.655****	.553*	-.021	.462*	.201	.059	-.262	-.390	**.577****	**.745****	**.857****	**.760****	1.000	**.825****	.034	.305	.192	**.706****	**.614****	**.570****	**.627****	**.596****	.288	.531*	.454*	**.562****	.045	.002
	Sig. (2-tailed)	.001	.011	.925	.040	.370	.804	.238	.089	.005	.000	.000	.000	.	.000	.884	.179	.416	.001	.002	.006	.003	.006	.194	.016	.034	.010	.843	.994
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Gait speed post fast	Correlation Coefficient	.396	.419	.012	.430	.271	.021	-.363	-.515*	.466*	**.574****	**.824****	**.931****	**.825****	1.000	.092	.365	.301	.493*	.555*	.526*	.397	.370	.299	**.579****	.407	.553*	.108	.235
	Sig. (2-tailed)	.084	.066	.960	.059	.248	.929	.116	.020	.038	.008	.000	.000	.000	.	.701	.114	.197	.027	.011	.017	.083	.108	.201	.007	.075	.011	.652	.318
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
RAPA 1 pre	Correlation Coefficient	-.329	-.426	-.125	-.226	-.012	.150	-.273	-.198	-.339	-.280	-.023	.048	.034	.092	1.000	.467*	.150	.023	-.214	-.131	-.137	-.105	.129	.174	-.348	-.418	.044	-.188
	Sig. (2-tailed)	.145	.061	.589	.337	.959	.527	.232	.402	.133	.232	.923	.842	.884	.701	.	.033	.529	.924	.352	.572	.564	.658	.577	.462	.123	.066	.850	.428
	N	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	21	20	20	21	21	20	20	21	20	21	20	21	20
RAPA 2 Pre	Correlation Coefficient	-.019	.047	-.108	.254	.008	-.180	-.417	**-.582****	.119	.246	.220	.350	.305	.365	.467*	1.000	.216	.388	.097	.160	.189	.243	.315	.463*	.080	.191	.108	.299
	Sig. (2-tailed)	.935	.844	.640	.279	.973	.446	.060	.007	.607	.296	.339	.130	.179	.114	.033	.	.360	.091	.675	.487	.425	.303	.165	.040	.729	.419	.642	.200
	N	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	21	20	20	21	21	20	20	21	20	21	20	21	20

		BCAM pre	BCAM post	C3Q pre	C3Q post	HADS-A pre	HADS-A post	HADS-D pre	HADS-D post	CB&;M pre	CB&;M post	Gait speed pre slow	Gait speed post slow	Gait speed pre fast	Gait speed post fast	RAPA 1 pre	RAPA 2 Pre	RAPA 1 post	RAPA 2 post	Steps/day pre	Km per day pre	Steps/day post	Km per day post	standard general health pre	standard general health post	standard physical pre	standard physical post	standard role pre	standard role post
RAPA 1 post	Correlation Coefficient	.079	.022	.575**	.538*	-.285	-.271	-.513*	-.563**	.233	.249	.119	.145	.192	.301	.150	.216	1.000	.253	.353	.423	.277	.378	.580**	.519*	.530*	.441	.174	.195
	Sig. (2-tailed)	.739	.927	.008	.014	.224	.248	.021	.010	.322	.290	.617	.543	.416	.197	.529	.360	.	.282	.127	.063	.237	.100	.007	.019	.016	.052	.464	.411
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
RAPA 2 post	Correlation Coefficient	.480*	.461*	.028	.607**	.118	-.040	-.328	-.433	.409	.527*	.679**	.437	.706**	.493*	.023	.388	.253	1.000	.604**	.571**	.537*	.504*	.135	.412	.353	.505*	-.149	.056
	Sig. (2-tailed)	.032	.041	.906	.005	.620	.868	.158	.056	.073	.017	.001	.054	.001	.027	.924	.091	.282	.	.005	.009	.015	.024	.571	.071	.127	.023	.530	.815
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Steps/day pre	Correlation Coefficient	.685**	.534*	.239	.502*	-.033	-.068	-.415	-.320	.705**	.750**	.659**	.484*	.614**	.555*	-.214	.097	.353	.604**	1.000	.976**	.878**	.848**	.482*	.619**	.676**	.722**	.194	.360
	Sig. (2-tailed)	.000	.015	.284	.024	.882	.775	.055	.169	.000	.000	.001	.031	.002	.011	.352	.675	.127	.005	.	.000	.000	.000	.023	.004	.001	.000	.387	.118
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Km per day pre	Correlation Coefficient	.660**	.504*	.291	.513*	-.057	-.087	-.468*	-.383	.695**	.714**	.616**	.459*	.570**	.526*	-.131	.160	.423	.571**	.976**	1.000	.829**	.857**	.501*	.621**	.647**	.652**	.222	.380
	Sig. (2-tailed)	.001	.023	.188	.021	.800	.717	.028	.096	.000	.000	.002	.042	.006	.017	.572	.487	.063	.009	.000	.	.000	.000	.018	.003	.001	.002	.320	.099
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Steps/day post	Correlation Coefficient	.747**	.472*	.073	.387	.037	.088	-.248	-.234	.736**	.791**	.566**	.341	.627**	.397	-.137	.189	.277	.537*	.878**	.829**	1.000	.962**	.475*	.508*	.668**	.641**	-.020	.139
	Sig. (2-tailed)	.000	.036	.761	.092	.877	.712	.292	.322	.000	.000	.009	.141	.003	.083	.564	.425	.237	.015	.000	.000	.	.000	.035	.022	.001	.002	.933	.560
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Km per day post	Correlation Coefficient	.715**	.450*	.145	.458*	.001	.015	-.284	-.310	.737**	.791**	.540*	.329	.596**	.370	-.105	.243	.378	.504*	.848**	.857**	.962**	1.000	.473*	.494*	.637**	.622**	.028	.156
	Sig. (2-tailed)	.000	.047	.541	.042	.997	.949	.224	.183	.000	.000	.014	.156	.006	.108	.658	.303	.100	.024	.000	.000	.000	.	.035	.027	.002	.003	.908	.511
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
standard general health pre	Correlation Coefficient	.452*	.260	.372	.260	-.502*	-.321	-.704**	-.454*	.551**	.401	.252	.188	.288	.299	.129	.315	.580**	.135	.482*	.501*	.475*	.473*	1.000	.812**	.674**	.315	.578**	.543*
	Sig. (2-tailed)	.035	.268	.088	.268	.017	.168	.000	.044	.008	.080	.257	.428	.194	.201	.577	.165	.007	.571	.023	.018	.035	.035	.	.000	.001	.177	.005	.013
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
standard general health post	Correlation Coefficient	.476*	.511*	.339	.523*	-.237	-.312	-.762**	-.629**	.605**	.555*	.514*	.467*	.531*	.579**	.174	.463*	.519*	.412	.619**	.621**	.508*	.494*	.812**	1.000	.615**	.569**	.533*	.596**
	Sig. (2-tailed)	.034	.021	.143	.018	.314	.181	.000	.003	.005	.011	.020	.038	.016	.007	.462	.040	.019	.071	.004	.003	.022	.027	.000	.	.004	.009	.016	.006
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

		BCAM pre	BCAM post	C3Q pre	C3Q post	HADS-A pre	HADS-A post	HADS-D pre	HADS-D post	CB&;M pre	CB&;M post	Gait speed pre slow	Gait speed post slow	Gait speed pre fast	Gait speed post fast	RAPA 1 pre	RAPA 2 Pre	RAPA 1 post	RAPA 2 post	Steps/day pre	Km per day pre	Steps/day post	Km per day post	standard general health pre	standard general health post	standard physical pre	standard physical post	standard role pre	standard role post
standard physical pre	Correlation Coefficient	**.698****	.519*	.463*	.537*	-.278	-.252	-.475*	-.406	**.723****	**.699****	.318	.287	.454*	.407	-.348	.080	.530*	.353	**.676****	**.647****	**.668****	**.637****	**.674****	**.615****	1.000	**.703****	.274	.422
	Sig. (2-tailed)	.000	.019	.030	.015	.210	.284	.025	.076	.000	.001	.150	.220	.034	.075	.123	.729	.016	.127	.001	.001	.001	.002	.001	.004	.	.001	.217	.064
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
standard physical post	Correlation Coefficient	.559*	.533*	.145	**.628****	.025	-.226	-.282	-.444*	**.734****	**.794****	.497*	.504*	**.562****	.553*	-.418	.191	.441	.505*	**.722****	**.652****	**.641****	**.622****	.315	**.569****	**.703****	1.000	.163	.392
	Sig. (2-tailed)	.010	.016	.543	.003	.917	.338	.228	.050	.000	.000	.026	.023	.010	.011	.066	.419	.052	.023	.000	.002	.002	.003	.177	.009	.001	.	.492	.087
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
standard role pre	Correlation Coefficient	.096	.302	.189	.249	**-.579****	**-.738****	-.492*	-.059	.372	.101	.000	.053	.045	.108	.044	.108	.174	-.149	.194	.222	-.020	.028	**.578****	.533*	.274	.163	1.000	**.661****
	Sig. (2-tailed)	.669	.196	.400	.290	.005	.000	.020	.804	.089	.670	1.000	.826	.843	.652	.850	.642	.464	.530	.387	.320	.933	.908	.005	.016	.217	.492	.	.002
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
standard role post	Correlation Coefficient	.122	.391	.227	.315	-.386	-.515*	**-.631****	-.337	.414	.309	.112	.243	.002	.235	-.188	.299	.195	.056	.360	.380	.139	.156	.543*	**.596****	.422	.392	**.661****	1.000
	Sig. (2-tailed)	.609	.089	.337	.177	.093	.020	.003	.146	.069	.185	.637	.302	.994	.318	.428	.200	.411	.815	.118	.099	.560	.511	.013	.006	.064	.087	.002	.
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Standard social pre	Correlation Coefficient	.115	.278	.377	.315	-.505*	-.486*	**-.669****	-.373	.238	-.052	-.028	.012	-.070	.057	-.071	.174	.156	.102	.220	.299	-.090	-.039	.396	.442	.277	.092	.474*	**.671****
	Sig. (2-tailed)	.609	.235	.084	.176	.016	.030	.001	.105	.286	.829	.902	.960	.758	.811	.759	.451	.510	.670	.326	.177	.707	.870	.068	.051	.211	.700	.026	.001
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Standard social post	Correlation Coefficient	**.653****	**.647****	.248	.522*	.012	-.038	-.558*	-.476*	**.727****	**.652****	**.600****	.538*	.524*	**.616****	-.198	.200	.369	.470*	**.823****	**.836****	**.662****	**.649****	.558	**.735****	**.685****	**.670****	.230	.485*
	Sig. (2-tailed)	.002	.002	.291	.018	.960	.874	.011	.034	.000	.002	.005	.014	.018	.004	.402	.399	.110	.036	.000	.000	.001	.002	.011	.000	.001	.001	.329	.030
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Standard cognitive pre	Correlation Coefficient	.099	.198	.458*	**.579****	**-.552****	**-.670****	-.464*	-.259	.350	.178	-.114	-.069	-.037	.023	-.128	.046	.485*	-.006	.406	.462*	.252	.358	.363	.369	.512*	.360	.517*	.443
	Sig. (2-tailed)	.661	.402	.032	.008	.008	.001	.030	.270	.111	.453	.614	.772	.869	.924	.579	.843	.030	.981	.061	.030	.284	.122	.097	.109	.015	.119	.014	.051
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Standard cognitive post	Correlation Coefficient	.114	.376	.075	**.621****	-.265	-.528*	-.358	-.492	.342	.391	.257	.377	.291	.391	-.189	.446*	.280	.238	.297	.320	.243	.320	.308	.356	.470*	.380	.337	.467*
	Sig. (2-tailed)	.633	.102	.755	.003	.259	.017	.121	.027	.140	.088	.274	.101	.214	.088	.424	.049	.232	.313	.204	.170	.303	.169	.186	.123	.037	.098	.146	.038
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

		BCAM pre	BCAM post	C3Q pre	C3Q post	HADS-A pre	HADS-A post	HADS-D pre	HADS-D post	CB&;M pre	CB&;M post	Gait speed pre slow	Gait speed post slow	Gait speed pre fast	Gait speed post fast	RAPA 1 pre	RAPA 2 Pre	RAPA 1 post	RAPA 2 post	Steps/day pre	Km per day pre	Steps/day post	Km per day post	standard general health pre	standard general health post	standard physical pre	standard physical post	standard role pre	standard role post
standard pain pre	Correlation Coefficient	.561**	.395	.240	.285	-.353	-.236	-.701**	-.451*	.653**	.549*	.350	.259	.418	.350	.087	.225	.378	.458*	.681**	.667**	.547*	.483*	.682**	.813**	.666**	.534*	.418	.498*
	Sig. (2-tailed)	.007	.085	.283	.223	.107	.317	.000	.046	.001	.012	.110	.270	.053	.131	.708	.327	.100	.042	.000	.001	.013	.031	.000	.000	.001	.015	.053	.026
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
standard pain post	Correlation Coefficient	.456*	.423	.414	.596**	-.310	-.384	-.712**	-.591**	.655**	.604**	.469*	.388	.377	.409	-.038	.244	.612**	.485*	.703**	.692**	.535*	.541*	.615**	.808**	.601**	.741**	.420	.523*
	Sig. (2-tailed)	.043	.063	.070	.006	.184	.094	.000	.006	.002	.005	.037	.091	.101	.074	.875	.300	.004	.030	.001	.001	.015	.014	.004	.000	.005	.000	.065	.018
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
standard mental pre	Correlation Coefficient	-.011	.086	.290	.181	-.771**	-.679**	-.715**	-.377	.261	.065	-.143	.014	-.135	-.013	.108	.184	.213	-.079	.162	.230	-.003	.076	.422	.430	.226	.032	.601**	.680**
	Sig. (2-tailed)	.961	.718	.190	.444	.000	.001	.000	.102	.241	.787	.525	.952	.549	.957	.642	.424	.367	.742	.471	.302	.990	.752	.050	.059	.312	.893	.003	.001
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
standard mental post	Correlation Coefficient	.211	.196	.538*	.575**	-.504*	-.591**	-.707**	-.492*	.327	.171	.281	.153	.181	.168	.233	.255	.477*	.382	.406	.511*	.211	.329	.393	.519*	.220	.191	.466*	.263
	Sig. (2-tailed)	.372	.407	.014	.008	.023	.006	.000	.028	.160	.472	.229	.521	.445	.480	.323	.279	.033	.096	.075	.021	.373	.156	.087	.019	.351	.420	.038	.263
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
standard energy pre	Correlation Coefficient	.250	.293	.511*	.527*	-.511*	-.454*	-.797**	-.499*	.399	.218	.194	.093	.215	.226	.262	.224	.599**	.225	.468*	.534*	.296	.357	.716**	.767**	.581**	.220	.601**	.540*
	Sig. (2-tailed)	.261	.210	.015	.017	.015	.044	.000	.025	.066	.356	.388	.697	.337	.339	.250	.329	.005	.341	.028	.010	.204	.122	.000	.000	.005	.351	.003	.014
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Standard energy post	Correlation Coefficient	.341	.239	.460*	.754**	-.115	-.242	-.658**	-.841**	.348	.471*	.580**	.484*	.532*	.531*	.184	.461*	.681**	.613**	.524*	.595**	.462*	.564**	.451*	.607**	.497*	.458*	.048	.193
	Sig. (2-tailed)	.141	.310	.042	.000	.628	.305	.002	.000	.132	.036	.007	.031	.016	.016	.437	.041	.001	.004	.018	.006	.040	.010	.046	.005	.026	.042	.841	.415
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
standard health distress pre	Correlation Coefficient	.385	.244	.169	.019	-.650**	-.437	-.656**	-.307	.603**	.483*	.129	.274	.167	.245	-.073	.089	.260	.034	.442*	.416	.403	.366	.626**	.570**	.515*	.356	.481*	.632**
	Sig. (2-tailed)	.076	.300	.451	.936	.001	.054	.001	.188	.003	.031	.568	.242	.458	.297	.753	.702	.267	.887	.039	.054	.078	.113	.002	.009	.014	.123	.023	.003
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Standard Health distress post	Correlation Coefficient	.398	.312	.511*	.586**	-.538*	-.667**	-.716**	-.516*	.619**	.489*	.305	.304	.271	.308	.012	.378	.554*	.245	.537*	.597**	.451*	.549*	.675**	.649**	.572**	.507*	.620**	.512*
	Sig. (2-tailed)	.082	.181	.021	.007	.014	.001	.000	.020	.004	.029	.192	.192	.248	.186	.959	.100	.011	.298	.015	.005	.046	.012	.001	.002	.008	.023	.004	.021
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

		BCAM pre	BCAM post	C3Q pre	C3Q post	HADS-A pre	HADS-A post	HADS-D pre	HADS-D post	CB&;M pre	CB&M post	Gait speed pre slow	Gait speed post slow	Gait speed pre fast	Gait speed post fast	RAPA 1 pre	RAPA 2 Pre	RAPA 1 post	RAPA 2 post	Steps/day pre	Km per day pre	Steps/day post	Km per day post	standard general health	standard general health	standard physical pre	standard physical post	standard role pre	standard role post
	Sig. (2-tailed)	.511	.328	.345	.103	.060	.003	.003	.071	.038	.213	.327	.240	.603	.311	.862	.106	.191	.511	.095	.049	.746	.497	.011	.033	.058	.289	.001	.001
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Standard QoL post	Correlation Coefficient	.510*	.402	.573**	.730**	-.452*	-.526*	-.729**	-.669**	.573**	.530*	.390	.279	.446*	.346	.034	.458*	.635**	.489*	.568**	.637**	.564**	.667**	.670**	.703**	.634**	.489*	.360	.387
	Sig. (2-tailed)	.022	.079	.008	.000	.046	.017	.000	.001	.008	.016	.089	.234	.049	.135	.887	.042	.003	.029	.009	.003	.010	.001	.001	.001	.003	.029	.119	.092
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
standard health transition pre	Correlation Coefficient	.200	.382	.209	.639**	-.062	-.422	-.264	-.241	.408	.344	.335	.355	.362	.463*	-.391	.283	.390	.383	.382	.359	.209	.228	.351	.337	.515*	.563**	.343	.481*
	Sig. (2-tailed)	.373	.096	.350	.002	.783	.064	.235	.306	.059	.138	.128	.124	.098	.040	.080	.213	.089	.096	.079	.101	.377	.335	.110	.146	.014	.010	.118	.032
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Standard health transition post	Correlation Coefficient	.140	.148	.112	.668**	.136	-.200	-.009	-.286	.120	.248	.453*	.234	.472*	.349	-.081	.176	.402	.490*	.367	.313	.402	.424	.095	.253	.201	.448*	-.013	-.220
	Sig. (2-tailed)	.555	.534	.640	.001	.567	.397	.970	.222	.614	.292	.045	.320	.036	.131	.733	.459	.079	.028	.112	.180	.079	.063	.691	.282	.394	.048	.956	.350
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Age	Correlation Coefficient	-.248	-.290	.215	-.165	-.365	-.392	-.345	-.154	-.015	-.067	-.218	.028	-.273	-.018	.399	.312	.186	-.477*	-.086	-.040	-.019	.044	.281	.316	-.089	-.111	.401	.326
	Sig. (2-tailed)	.266	.215	.336	.487	.094	.087	.116	.516	.946	.780	.330	.907	.219	.940	.073	.169	.432	.033	.703	.861	.937	.852	.205	.174	.692	.642	.064	.160
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
Year diagnosed	Correlation Coefficient	.483*	.373	-.230	.299	.389	.200	.005	-.437	.301	.657**	.588**	.465*	.675**	.434	-.033	.317	.015	.712**	.396	.387	.474*	.474*	-.021	.309	.148	.457*	-.254	-.070
	Sig. (2-tailed)	.023	.105	.302	.200	.073	.399	.981	.054	.174	.002	.004	.039	.001	.056	.886	.161	.951	.000	.068	.076	.035	.035	.925	.186	.510	.043	.255	.769
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20
CD4	Correlation Coefficient	.544*	.270	.091	-.218	-.068	.069	-.189	.031	.330	.195	.347	.368	.361	.354	.099	-.086	-.192	.142	.115	.128	.079	.068	.246	.193	.053	-.259	.104	.122
	Sig. (2-tailed)	.024	.331	.729	.434	.795	.807	.468	.912	.195	.486	.173	.177	.154	.196	.715	.753	.493	.614	.659	.625	.781	.810	.341	.492	.840	.351	.691	.665
	N	17	15	17	15	17	15	17	15	17	15	17	15	17	15	16	16	15	15	17	17	15	15	17	15	17	15	17	15
Years with HIV	Correlation Coefficient	-.508*	-.388	.204	-.294	-.312	-.137	.020	.435	-.345	-.671**	-.528*	-.373	-.629**	-.340	.055	-.360	-.032	-.679**	-.406	-.406	-.509*	-.524*	-.047	-.342	-.175	-.455*	.207	.016
	Sig. (2-tailed)	.016	.091	.363	.209	.158	.564	.930	.056	.116	.001	.012	.105	.002	.142	.814	.109	.893	.001	.061	.061	.022	.018	.836	.139	.435	.044	.356	.947
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	21	21	20	20	22	22	20	20	22	20	22	20	22	20

		Standard social pre	Standard social post	Standard cognitive pre	Standard cognitive post	standard pain pre	standard pain post	standard mental pre	standard mental post	standard energy pre	Standard energy post	standard health distress pre	Standard Health distress post	Standard QoL pre	Standard QoL post	standard health transition pre	Standard health transition post	Age	Year diagnosed	CD4	Years with HIV
BCAM pre	Correlation Coefficient	.115	.653**	.099	.114	.561**	.456*	-.011	.211	.250	.341	.385	.398	.148	.510*	.200	.140	-.248	.483*	.544*	-.508*
	Sig. (2-tailed)	.609	.002	.661	.633	.007	.043	.961	.372	.261	.141	.076	.082	.511	.022	.373	.555	.266	.023	.024	.016
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
BCAM post	Correlation Coefficient	.278	.647**	.198	.376	.395	.423	.086	.196	.293	.239	.244	.312	.230	.402	.382	.148	-.290	.373	.270	-.388
	Sig. (2-tailed)	.235	.002	.402	.102	.085	.063	.718	.407	.210	.310	.300	.181	.328	.079	.096	.534	.215	.105	.331	.091
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
C3Q pre	Correlation Coefficient	.377	.248	.458*	.075	.240	.414	.290	.538*	.511*	.460*	.169	.511*	.211	.573**	.209	.112	.215	-.230	.091	.204
	Sig. (2-tailed)	.084	.291	.032	.755	.283	.070	.190	.014	.015	.042	.451	.021	.345	.008	.350	.640	.336	.302	.729	.363
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
C3Q post	Correlation Coefficient	.315	.522*	.579**	.621**	.285	.596**	.181	.575**	.527*	.754**	.019	.586**	.375	.730**	.639**	.668**	-.165	.299	-.218	-.294
	Sig. (2-tailed)	.176	.018	.008	.003	.223	.006	.444	.008	.017	.000	.936	.007	.103	.000	.002	.001	.487	.200	.434	.209
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
HADS-A pre	Correlation Coefficient	-.505*	.012	-.552**	-.265	-.353	-.310	-.771**	-.504*	-.511*	-.115	-.650**	-.538*	-.407	-.452*	-.062	.136	-.365	.389	-.068	-.312
	Sig. (2-tailed)	.016	.960	.008	.259	.107	.184	.000	.023	.015	.628	.001	.014	.060	.046	.783	.567	.094	.073	.795	.158
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
HADS-A post	Correlation Coefficient	-.486*	-.038	-.670**	-.528*	-.236	-.384	-.679**	-.591**	-.454*	-.242	-.437	-.667**	-.625**	-.526*	-.422	-.200	-.392	.200	.069	-.137
	Sig. (2-tailed)	.030	.874	.001	.017	.317	.094	.001	.006	.044	.305	.054	.001	.003	.017	.064	.397	.087	.399	.807	.564
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
HADS-D pre	Correlation Coefficient	-.669**	-.558*	-.464*	-.358	-.701**	-.712**	-.715**	-.707**	-.797**	-.658**	-.656**	-.716**	-.596**	-.729**	-.264	-.009	-.345	.005	-.189	.020
	Sig. (2-tailed)	.001	.011	.030	.121	.000	.000	.000	.000	.000	.002	.001	.000	.003	.000	.235	.970	.116	.981	.468	.930
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
HADS-D post	Correlation Coefficient	-.373	-.476*	-.259	-.492*	-.451*	-.591**	-.377	-.492*	-.499*	-.841**	-.307	-.516*	-.412	-.669**	-.241	-.286	-.154	-.437	.031	.435
	Sig. (2-tailed)	.105	.034	.270	.027	.046	.006	.102	.028	.025	.000	.188	.020	.071	.001	.306	.222	.516	.054	.912	.056
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
CB&;M pre	Correlation Coefficient	.238	.727**	.350	.342	.653**	.655**	.261	.327	.399	.348	.603**	.619**	.445*	.573**	.408	.120	-.015	.301	.330	-.345
	Sig. (2-tailed)	.286	.000	.111	.140	.001	.002	.241	.160	.066	.132	.003	.004	.038	.008	.059	.614	.946	.174	.195	.116
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
CB&;M post	Correlation Coefficient	-.052	.652**	.178	.391	.549*	.604**	.065	.171	.218	.471*	.483*	.489*	.291	.530*	.344	.248	-.067	.657**	.195	-.671**
	Sig. (2-tailed)	.829	.002	.453	.088	.012	.005	.787	.472	.356	.036	.031	.029	.213	.016	.138	.292	.780	.002	.486	.001
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
Gait speed pre slow	Correlation Coefficient	-.028	.600**	-.114	.257	.350	.469*	-.143	.281	.194	.580**	.129	.305	.219	.390	.335	.453*	-.218	.588**	.347	-.528*
	Sig. (2-tailed)	.902	.005	.614	.274	.110	.037	.525	.229	.388	.007	.568	.192	.327	.089	.128	.045	.330	.004	.173	.012
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22

		Standard social pre	Standard social post	Standard cognitive pre	Standard cognitive post	standard pain pre	standard pain post	standard mental pre	standard mental post	standard energy pre	Standard energy post	standard health distress pre	Standard Health distress post	Standard QoL pre	Standard QoL post	standard health transition pre	Standard health transition post	Age	Year diagnosed	CD4	Years with HIV
Gait speed post slow	Correlation Coefficient	.012	.538*	-.069	.377	.259	.388	.014	.153	.093	.484*	.274	.304	.275	.279	.355	.234	.028	.465*	.368	-.373
	Sig. (2-tailed)	.960	.014	.772	.101	.270	.091	.952	.521	.697	.031	.242	.192	.240	.234	.124	.320	.907	.039	.177	.105
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
Gait speed pre fast	Correlation Coefficient	-.070	.524*	-.037	.291	.418	.377	-.135	.181	.215	.532*	.167	.271	.117	.446*	.362	.472*	-.273	.675**	.361	-.629**
	Sig. (2-tailed)	.758	.018	.869	.214	.053	.101	.549	.445	.337	.016	.458	.248	.603	.049	.098	.036	.219	.001	.154	.002
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Gait speed post fast	Correlation Coefficient	.057	.616**	.023	.391	.350	.409	-.013	.168	.226	.531*	.245	.308	.239	.346	.463*	.349	-.018	.434	.354	-.340
	Sig. (2-tailed)	.811	.004	.924	.088	.131	.074	.957	.480	.339	.016	.297	.186	.311	.135	.040	.131	.940	.056	.196	.142
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
RAPA 1 pre	Correlation Coefficient	-.071	-.198	-.128	-.189	.087	-.038	.108	.233	.262	.184	-.073	.012	-.040	.034	-.391	-.081	.399	-.033	.099	.055
	Sig. (2-tailed)	.759	.402	.579	.424	.708	.875	.642	.323	.250	.437	.753	.959	.862	.887	.080	.733	.073	.886	.715	.814
	N	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	21	16	21
RAPA 2 Pre	Correlation Coefficient	.174	.200	.046	.446*	.225	.244	.184	.255	.224	.461*	.089	.378	.363	.458*	.283	.176	.312	.317	-.086	-.360
	Sig. (2-tailed)	.451	.399	.843	.049	.327	.300	.424	.279	.329	.041	.702	.100	.106	.042	.213	.459	.169	.161	.753	.109
	N	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	20	21	21	16	21
RAPA 1 post	Correlation Coefficient	.156	.369	.485*	.280	.378	.612**	.213	.477*	.599**	.681**	.260	.554*	.305	.635**	.390	.402	.186	.015	-.192	-.032
	Sig. (2-tailed)	.510	.110	.030	.232	.100	.004	.367	.033	.005	.001	.267	.011	.191	.003	.089	.079	.432	.951	.493	.893
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
RAPA 2 post	Correlation Coefficient	.102	.470*	-.006	.238	.458*	.485*	-.079	.382	.225	.613**	.034	.245	.156	.489*	.383	.490*	-.477*	.712**	.142	-.679**
	Sig. (2-tailed)	.670	.036	.981	.313	.042	.030	.742	.096	.341	.004	.887	.298	.511	.029	.096	.028	.033	.000	.614	.001
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
Steps/day pre	Correlation Coefficient	.220	.823**	.406	.297	.681**	.703**	.162	.406	.468*	.524*	.442*	.537*	.365	.568**	.382	.367	-.086	.396	.115	-.406
	Sig. (2-tailed)	.326	.000	.061	.204	.000	.001	.471	.075	.028	.018	.039	.015	.095	.009	.079	.112	.703	.068	.659	.061
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Km per day pre	Correlation Coefficient	.299	.836**	.462*	.320	.667**	.692**	.230	.511*	.534*	.595**	.416	.597**	.424*	.637**	.359	.313	-.040	.387	.128	-.406
	Sig. (2-tailed)	.177	.000	.030	.170	.001	.001	.302	.021	.010	.006	.054	.005	.049	.003	.101	.180	.861	.076	.625	.061
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Steps/day post	Correlation Coefficient	-.090	.662**	.252	.243	.547*	.535*	-.003	.211	.296	.462*	.403	.451*	.077	.564**	.209	.402	-.019	.474*	.079	-.509*
	Sig. (2-tailed)	.707	.001	.284	.303	.013	.015	.990	.373	.204	.040	.078	.046	.746	.010	.377	.079	.937	.035	.781	.022
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
Km per day post	Correlation Coefficient	-.039	.649**	.358	.320	.483*	.541*	.076	.329	.357	.564**	.366	.549*	.161	.667**	.228	.424	.044	.474*	.068	-.524*
	Sig. (2-tailed)	.870	.002	.122	.169	.031	.014	.752	.156	.122	.010	.113	.012	.497	.001	.335	.063	.852	.035	.810	.018
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20

		Standard social pre	Standard social post	Standard cognitive pre	Standard cognitive post	standard pain pre	standard pain post	standard mental pre	standard mental post	standard energy pre	Standard energy post	standard health distress pre	Standard Health distress post	Standard QoL pre	Standard QoL post	standard health transition pre	Standard health transition post	Age	Year diagnosed	CD4	Years with HIV
standard general health pre	Correlation Coefficient	.396	.558*	.363	.308	.682**	.615**	.422	.393	.716**	.451*	.626**	.675**	.529*	.670**	.351	.095	.281	-.021	.246	-.047
	Sig. (2-tailed)	.068	.011	.097	.186	.000	.004	.050	.087	.000	.046	.002	.001	.011	.001	.110	.691	.205	.925	.341	.836
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
standard general health post	Correlation Coefficient	.442	.735**	.369	.356	.813**	.808**	.430	.519*	.767**	.607**	.570**	.649**	.478*	.703**	.337	.253	.316	.309	.193	-.342
	Sig. (2-tailed)	.051	.000	.109	.123	.000	.000	.059	.019	.000	.005	.009	.002	.033	.001	.146	.282	.174	.186	.492	.139
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
standard physical pre	Correlation Coefficient	.277	.685**	.512*	.470*	.666**	.601**	.226	.220	.581**	.497*	.515*	.572**	.409	.634**	.515*	.201	-.089	.148	.053	-.175
	Sig. (2-tailed)	.211	.001	.015	.037	.001	.005	.312	.351	.005	.026	.014	.008	.058	.003	.014	.394	.692	.510	.840	.435
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
standard physical post	Correlation Coefficient	.092	.670**	.360	.380	.534*	.741**	.032	.191	.220	.458*	.356	.507*	.250	.489*	.563**	.448*	-.111	.457*	-.259	-.455*
	Sig. (2-tailed)	.700	.001	.119	.098	.015	.000	.893	.420	.351	.042	.123	.023	.289	.029	.010	.048	.642	.043	.351	.044
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
standard role pre	Correlation Coefficient	.474*	.230	.517*	.337	.418	.420	.601**	.466*	.601**	.048	.481*	.620**	.658**	.360	.343	-.013	.401	-.254	.104	.207
	Sig. (2-tailed)	.026	.329	.014	.146	.053	.065	.003	.038	.003	.841	.023	.004	.001	.119	.118	.956	.064	.255	.691	.356
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
standard role post	Correlation Coefficient	.671**	.485*	.443	.467*	.498*	.523*	.680**	.263	.540*	.193	.632**	.512*	.672**	.387	.481*	-.220	.326	-.070	.122	.016
	Sig. (2-tailed)	.001	.030	.051	.038	.026	.018	.001	.263	.014	.415	.003	.021	.001	.092	.032	.350	.160	.769	.665	.947
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
Standard social pre	Correlation Coefficient	1.000	.433	.487*	.312	.453*	.328	.745**	.504*	.613**	.284	.423*	.378	.436*	.448*	.215	-.215	.071	-.158	.245	.116
	Sig. (2-tailed)	.	.057	.022	.180	.034	.158	.000	.023	.002	.225	.050	.101	.043	.048	.336	.363	.755	.484	.343	.607
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Standard social post	Correlation Coefficient	.433	1.000	.306	.291	.725**	.706**	.214	.406	.503*	.544*	.445*	.564**	.354	.578**	.320	.251	.016	.384	.123	-.387
	Sig. (2-tailed)	.057	.	.190	.213	.000	.001	.364	.075	.024	.013	.049	.010	.125	.008	.169	.286	.946	.095	.663	.092
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
Standard cognitive pre	Correlation Coefficient	.487*	.306	1.000	.609**	.339	.450*	.663**	.599**	.710**	.431	.368	.677**	.485*	.621**	.313	.231	.313	-.292	-.420	.236
	Sig. (2-tailed)	.022	.190	.	.004	.123	.047	.001	.005	.000	.058	.092	.001	.022	.003	.156	.327	.157	.187	.093	.291
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Standard cognitive post	Correlation Coefficient	.312	.291	.609**	1.000	.090	.228	.484*	.286	.387	.515*	.329	.498*	.568**	.574**	.564**	.283	.103	.099	-.193	-.125
	Sig. (2-tailed)	.180	.213	.004	.	.706	.333	.030	.222	.092	.020	.157	.025	.009	.008	.010	.226	.667	.677	.492	.600
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
standard pain pre	Correlation Coefficient	.453*	.725**	.339	.090	1.000	.781**	.413	.464*	.660**	.404	.659**	.526*	.418	.530*	.164	.032	.099	.327	.159	-.357
	Sig. (2-tailed)	.034	.000	.123	.706	.	.000	.056	.039	.001	.077	.001	.017	.053	.016	.466	.893	.662	.137	.542	.103
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22

		Standard social pre	Standard social post	Standard cognitive pre	Standard cognitive post	standard pain pre	standard pain post	standard mental pre	standard mental post	standard energy pre	Standard energy post	standard health distress pre	Standard Health distress post	Standard QoL pre	Standard QoL post	standard health transition pre	Standard health transition post	Age	Year diagnosed	CD4	Years with HIV
standard pain post	Correlation Coefficient	.328	.706**	.450*	.228	.781**	1.000	.333	.640**	.635**	.616**	.507*	.753**	.514*	.669**	.368	.367	.240	.284	-.139	-.310
	Sig. (2-tailed)	.158	.001	.047	.333	.000	.	.151	.002	.003	.004	.023	.000	.020	.001	.111	.112	.309	.225	.620	.184
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
standard mental pre	Correlation Coefficient	.745**	.214	.663**	.484*	.413	.333	1.000	.548*	.646**	.284	.706**	.517*	.505*	.509*	.058	-.247	.468*	-.266	.193	.203
	Sig. (2-tailed)	.000	.364	.001	.030	.056	.151	.	.012	.001	.225	.000	.020	.017	.022	.798	.294	.028	.231	.459	.366
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
standard mental post	Correlation Coefficient	.504*	.406	.599**	.286	.464*	.640**	.548*	1.000	.712**	.688**	.252	.777**	.562**	.755**	.154	.408	.364	.078	.030	-.114
	Sig. (2-tailed)	.023	.075	.005	.222	.039	.002	.012	.	.000	.001	.283	.000	.010	.000	.518	.074	.115	.745	.917	.631
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
standard energy pre	Correlation Coefficient	.613**	.503*	.710**	.387	.660**	.635**	.646**	.712**	1.000	.624**	.438*	.670**	.594**	.729**	.330	.096	.240	-.122	-.010	.084
	Sig. (2-tailed)	.002	.024	.000	.092	.001	.003	.001	.000	.	.003	.042	.001	.004	.000	.134	.688	.283	.587	.970	.710
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Standard energy post	Correlation Coefficient	.284	.544*	.431	.515*	.404	.616**	.284	.688**	.624**	1.000	.175	.638**	.366	.851**	.353	.575**	.074	.418	.001	-.409
	Sig. (2-tailed)	.225	.013	.058	.020	.077	.004	.225	.001	.003	.	.461	.002	.112	.000	.127	.008	.757	.067	.997	.073
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
standard health distress pre	Correlation Coefficient	.423*	.445*	.368	.329	.659**	.507*	.706**	.252	.438*	.175	1.000	.510*	.351	.445*	.063	-.220	.374	-.032	.353	-.014
	Sig. (2-tailed)	.050	.049	.092	.157	.001	.023	.000	.283	.042	.461	.	.022	.110	.049	.781	.351	.086	.888	.164	.950
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Standard Health distress post	Correlation Coefficient	.378	.564**	.677**	.498*	.526*	.753**	.517*	.777**	.670**	.638**	.510*	1.000	.693**	.836**	.414	.404	.544*	.048	-.124	-.107
	Sig. (2-tailed)	.101	.010	.001	.025	.017	.000	.020	.000	.001	.002	.022	.	.001	.000	.070	.077	.013	.841	.661	.653
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
Standard QoL pre	Correlation Coefficient	.436*	.354	.485*	.568**	.418	.514*	.505*	.562**	.594**	.366	.351	.693**	1.000	.458*	.628**	.026	.237	-.071	-.026	.033
	Sig. (2-tailed)	.043	.125	.022	.009	.053	.020	.017	.010	.004	.112	.110	.001	.	.042	.002	.913	.288	.753	.921	.884
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Standard QoL post	Correlation Coefficient	.448*	.578**	.621**	.574**	.530*	.669**	.509*	.755**	.729**	.851**	.445*	.836**	.458*	1.000	.380	.488*	.257	.277	.107	-.344
	Sig. (2-tailed)	.048	.008	.003	.008	.016	.001	.022	.000	.000	.000	.049	.000	.042	.	.099	.029	.274	.236	.704	.137
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20
standard health transition pre	Correlation Coefficient	.215	.320	.313	.564**	.164	.368	.058	.154	.330	.353	.063	.414	.628**	.380	1.000	.392	-.149	-.043	-.081	.035
	Sig. (2-tailed)	.336	.169	.156	.010	.466	.111	.798	.518	.134	.127	.781	.070	.002	.099	.	.088	.509	.850	.758	.876
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Standard health transition post	Correlation Coefficient	-.215	.251	.231	.283	.032	.367	-.247	.408	.096	.575**	-.220	.404	.026	.488*	.392	1.000	-.057	.345	-.390	-.323
	Sig. (2-tailed)	.363	.286	.327	.226	.893	.112	.294	.074	.688	.008	.351	.077	.913	.029	.088	.	.813	.136	.150	.164
	N	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	15	20

		Standard social pre	Standard social post	Standard cognitive pre	Standard cognitive post	standard pain pre	standard pain post	standard mental pre	standard mental post	standard energy pre	Standard energy post	standard health distress pre	Standard Health distress post	Standard QoL pre	Standard QoL post	standard health transition pre	Standard health transition post	Age	Year diagnosed	CD4	Years with HIV
Age	Correlation Coefficient	.071	.016	.313	.103	.099	.240	.468*	.364	.240	.074	.374	.544*	.237	.257	-.149	-.057	1.000	-.389	-.057	.338
	Sig. (2-tailed)	.755	.946	.157	.667	.662	.309	.028	.115	.283	.757	.086	.013	.288	.274	.509	.813	.	.074	.828	.123
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
Year diagnosed	Correlation Coefficient	-.158	.384	-.292	.099	.327	.284	-.266	.078	-.122	.418	-.032	.048	-.071	.277	-.043	.345	-.389	1.000	.219	**-.986****
	Sig. (2-tailed)	.484	.095	.187	.677	.137	.225	.231	.745	.587	.067	.888	.841	.753	.236	.850	.136	.074	.	.397	.000
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22
CD4	Correlation Coefficient	.245	.123	-.420	-.193	.159	-.139	.193	.030	-.010	.001	.353	-.124	-.026	.107	-.081	-.390	-.057	.219	1.000	-.219
	Sig. (2-tailed)	.343	.663	.093	.492	.542	.620	.459	.917	.970	.997	.164	.661	.921	.704	.758	.150	.828	.397	.	.397
	N	17	15	17	15	17	15	17	15	17	15	17	15	17	15	17	15	17	17	17	17
Years with HIV	Correlation Coefficient	.116	-.387	.236	-.125	-.357	-.310	.203	-.114	.084	-.409	-.014	-.107	.033	-.344	.035	-.323	.338	**-.986****	-.219	1.000
	Sig. (2-tailed)	.607	.092	.291	.600	.103	.184	.366	.631	.710	.073	.950	.653	.884	.137	.876	.164	.123	.000	.397	.
	N	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	20	22	22	17	22

**. Correlation is significant at the 0.01 level (2-tailed) and is bolded.
*. Correlation is significant at the 0.05 level (2-tailed).