Full Title:	Understanding and Optimizing Brain Health in HIV Now
Abbreviated Title:	Positive Brain Health Now
Version Number:	V3.0
Date of Protocol:	April 1, 2014
Sponsor:	McGill University
Funding:	Canadian Institute of Health Research (CIHR)
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APPROVED	
Principal Investigator	Dr. Marie-Josée Brouillette
Signature	
Date	

PROTOCOL SUMMARY

Full Title	Understanding and Optimizing Brain Health in HIV Now
Short Title	Positive Brain Health Now
Sponsor	McGill University
Funding	Canadian Institute of Health Research (CIHR)
Principal Investigators	Dr. Marie-Josée Brouillette & Dr. Lesley Fellows
Primary Objective	To estimate the extent to which HIV-related clinical factors and patient centered outcomes relevant to brain health and its consequences inter-relate and evolve over time using a brief cognitive ability measure (B-CAM).
Secondary Objectives	(i) To contribute evidence for the validity of a brief brain health assessment approach combining both patient-reported and measured cognitive deficits; (ii) To estimate the accuracy of a brief cognitive ability measure (B-CAM) against standard neuropsychological testing; (iii) To contribute evidence for the feasibility, effectiveness potential, and acceptability of promising interventions for optimizing brain health; (iv) To explore the mechanisms underpinning longitudinal change in brain health.
Study Population	Inclusion Criteria • Age ≥ 35 (If necessary, we will oversample patients > 60 years old and women to ensure at least 100 of each are enrolled). • HIV+ for at least 1 year • Able to communicate adequately in either French or English • Able to give written informed consent Exclusion Criteria • Dementia (MSK-rating stage 3 or more-cognitive component only) • Concern about capacity to consent • Life expectancy of < 3 years or other personal factor limiting the ability to participate in follow-up • Non-HIV-related neurological disorder likely to affect cognition • Known active CNS opportunistic infection or hepatitis C requiring IFN treatment during the follow-up period • Known psychotic disorder • Current substance dependence or abuse within the past 12 months.
Study Design	Observational, Prospective Cohort
Sample Size	900
Accrual Period	24 months
Study Duration	27 months

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BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Background Information

People living with HIV worry about their memory, and with good reason. As their life expectancy increases, it is becoming clear that this chronic illness affects both cognition and mental health, even with excellent systemic viral control. Although we are only beginning to understand these emerging co-morbidities, they are likely the result of multiple interacting processes. HIV has direct effects on the brain: highly active anti-retroviral therapy (HAART) may not fully penetrate the CNS, providing a reservoir for viral replication, and inflammation may affect brain function[1]. Anti-retrovirals may themselves be neurotoxic[2-4], as may common co-morbidities such as aging, depression, cerebrovascular disease, substance abuse and hepatitis C infection. The experience of living with chronic infection can threaten brain health by affecting stress levels, coping, physical health, and social supports.

Although the burden of poor brain health in HIV in Canada is unknown, it is likely to be high. Recent studies in other developed countries, using comprehensive neuropsychological assessment, report a prevalence of (primarily mild) cognitive impairment of 30-50% [5,6]. Even higher rates have been documented in those over the age of 50, a rapidly expanding group at the frontier of existing knowledge about the combined effects of aging and longstanding HIV infection[7]. Depression is also common in HIV infection, with population-based prevalence of major depressive disorder estimated as high as 36%[8]. Mood disorders can affect cognition even in otherwise healthy individuals [9]. In HIV specifically, cognitive complaints have been associated with depressive symptoms more consistently than with objective cognitive performance[10]. It may be that depressive symptoms and cognitive difficulties are two facets of brain dysfunction, or that depression affects cognitive performance (in life and in testing situations) through effects on attention or motivation[11]. Impaired cognition and depression, whether together or separately, strike patients in their productive years, and can affect medication adherence, occupational and social function, quality of life, and even accelerate mortality[12-18]. Progress in understanding the heterogeneous, multi-factorial nature of compromised brain health in HIV will require careful clinical characterization, including of its evolution over time, accompanied by hypothesis-driven research focused on specific clinical phenotypes. Progress in predicting, treating and mitigating the impact of poor brain health will require better, practical clinical tools and evidence-based interventions specifically tailored for people living with HIV.

The nomenclature describing cognitive impairment, and the modalities used to measure cognition vary across clinical disciplines, hindering interdisciplinary research. For this study, we have chosen to use the term cognitive deficit and its positive opposite, cognitive ability; we also distinguish between directly measured cognitive deficits (i.e. neuropsychological tests) and perceived cognitive deficits reported as symptoms (here measured using validated questionnaires). This method is broadly consistent with the requirements of the current diagnostic criteria for HIV-Associated Neurocognitive Disorders (HAND)[2]. Our view of cognition departs from current diagnostic approaches by focusing on cognitive ability as a "quantity". We propose that declines in cognitive ability compared to the individual's own baseline will be the most useful trigger for intervention, and that stability or improvements are likely to be more important to the patient than whether they meet arbitrary diagnostic thresholds. Rigid use of diagnostic categories may prevent recognition of real difficulties, and limit access to useful interventions for patients with high (but deteriorating) cognitive abilities[19].

Current approaches to diagnosis rely on neuropsychological testing. This is resource-intensive and not universally available in the Canadian context. Front-line health care providers who must judge whom and when to refer are poorly equipped to respond to patients' concerns about cognition: What symptoms signal difficulties that warrant further investigation or intervention? What interventions are

appropriate? Are there patients who do not report symptoms who nonetheless have deficits and would benefit from assessment and treatment? How should they be identified? We recognize that a key challenge in this area is to understand the link between what patients are saying, which is what matters to them, and what the objective tests indicate. Developing better ways to measure both symptoms and signs that are feasible in everyday practice, and tuned to the full range of abilities in the population is a crucial first step. While better measurement and thorough description of the clinical phenomenology and its evolution are necessary, they are not sufficient. We need to link this level of study to work on the underlying pathogenic mechanisms if we are to develop rational approaches to treatment.

Our overall objective of this study is to identify, understand and optimize brain health in HIV. The following protocol will describe the study design of the main platform. The information collected during this stage will provide insights into the determinants and evolution of brain health and will address how to improve brain health measurement in clinical practice. This platform will also allow a sampling strategy, based on cohort multiple randomized controlled trials design[20], to identify people who would be eligible for entering pilot studies of promising interventions (Fig. 1). This approach uses the strength of a large, epidemiologically designed, observational study to provide a representative sample that can be characterized prospectively to answer questions about the evolution of outcomes of interest. In turn, sub-groups of the sample are identified for whom the pilot testing of specific interventions would provide pragmatic evidence for feasibility, effectiveness, and acceptability to patients. This will be a powerful platform for validating novel measurement approaches, providing needed estimates of the burden and heterogeneity of cognitive impairment over time, and for hypothesis driven research on mechanisms and interventions. The findings from this work will be both rigorous and generalizable and will directly inform HIV care in the Canadian context and beyond.

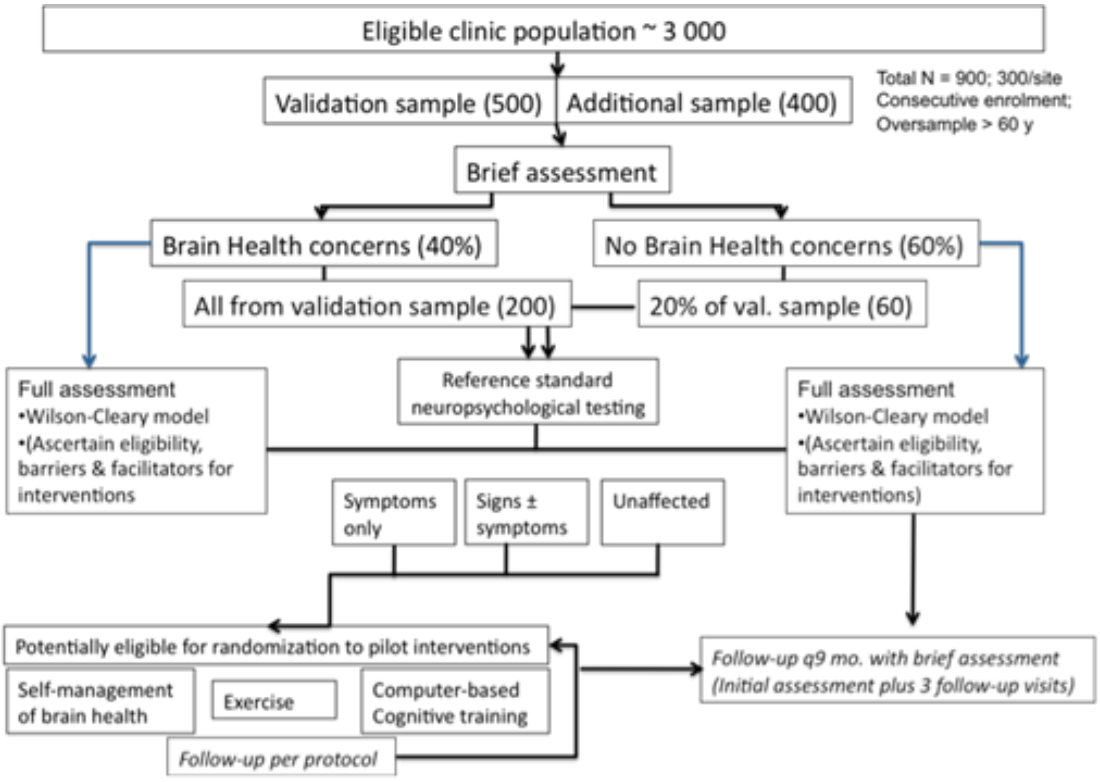

Fig. 1: Research Platform, including its use as a sampling frame for intervention development and piloting.

Measurement framework and instruments

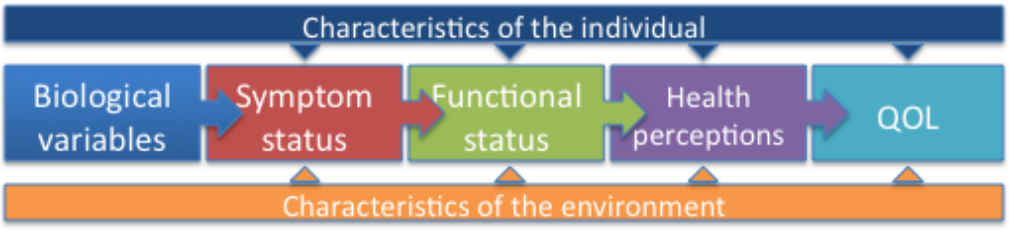

Fig. 2: Wilson-Cleary outcome model. Characteristics of the individual include motivation, symptom amplification; characteristics of the environment include psychological and social supports.

Our primary objective will require us to apply a theory-based measurement framework, permitting a comprehensive approach to understanding brain health in HIV. The Wilson-Cleary (WC) outcome model will be used to structure the core platform (Fig. 2). This model is widely used to assess the life impact of medical conditions. It comprehensively considers the relationship between characteristics of the individual, and of their environment, as they relate to a continuum from biological variables, to symptoms, to functional status and quality of life [21]. While the proposed work has a strong a priori focus on brain health, the use of a theoretical model for the measurement framework ensures that all important components of the health impact of HIV will be captured: this will also allow an understanding of the relative importance of brain health issues within the whole spectrum of HIV-associated health impact. Table 1 shows the elements to be collected on all patients. We have situated the brain health measures within the 'symptom' and 'function' components of the W-C model. The questionnaires we have chosen are all brief, well known in the health literature, and widely tested in various populations, permitting comparisons across health conditions. To assure wide application to the broader clinical context, we selected measures that are in the public domain and available in English and French.

<table>
<tr><td colspan="5">Characteristics of the individual
Age, sex, self-declared race, height, weight, education,
Lifestyle questionnaire: Smoking, work status, occupation, living situation , alcohol and drug use
Coping; healthy eating behaviour</td></tr>
<tr><td>Biological and physiological variables</td><td>Symptom status</td><td>Functional status</td><td>Health Perception</td><td>Quality of life</td></tr>
<tr><td rowspan="3">Nadir CD4+, current immunological markers, current viral load, peak viral load, current ARV treatment, duration of HIV infection;
Co-morbidities: diabetes, cardiovascular disease, hypercholesterolemia, hepatitis B & C, vitamin B12, TSH, others
(See Budget Justification for full list of laboratory measures)
Medications</td><td>Physical Symptoms: vitality, pain, sleep quality, HIV related signs and symptoms</td><td>Measured and PRO cognitive deficits; cognitive ability; self-efficacy</td><td rowspan="3">General health perception; health utility</td><td rowspan="3">Personalized quality of life; HIV-specific QOL</td></tr>
<tr><td>Emotional symptoms: anxiety, depression, apathy</td><td>Physical activity; physical function; self-efficacy</td></tr>
<tr><td></td><td>Role participation: work, illness intrusiveness, usual activities</td></tr>
<tr><td colspan="5">Social and psychological supports
Social Support, Self-management priorities</td></tr>
</table>

Table 1. Constructs & Measures Included in the Brain Health Platform

Platform cognitive measures: Measurement of cognitive ability is central to this proposal. This poses a problem that echoes the problems HIV clinicians are facing every day with their patients: How to measure cognitive ability with sufficient accuracy for research (or clinical) purposes, while minimizing the time burden to participants and the cost to research funders and the health care system? The ideal would not rely solely on patient report or on lengthy neuropsychological testing, and would provide information that can be used to accurately monitor change over time. We will apply a novel brief cognitive ability measure (B-CAM) which combines self-report and objective items within a single, ruler-like measure of cognitive ability. This provides a research quality measure of cognition that can be readily applied in the clinic, a tool we believe is absolutely vital to the evidence-based management of cognitive issues in HIV. B-CAM does not allow the diagnosis of HAND, which could limit how the knowledge gained through the proposed work can be related to the existing literature. We will therefore administer neuropsychological testing to a validation subset of the full cohort, allowing the diagnostic sensitivity and specificity of the B-CAM to be estimated against the reference standard.

The core platform and intervention studies will also rely on the B-CAM, a computerized tool to measure cognitive ability. The building blocks of this cognitive tool have been programmed onto Inquisit, a password protected site commercially available software that is used by behavioral scientists throughout the world for creating and administering numerous cognitive, social, and neuropsychological measures. It combines performance-based cognitive tasks and questions probing the domains of attention, concentration, memory, working memory, executive functions and language. Users access the Inquisit website and, from there, access our password protected battery. Patients will be identified only by subject ID numbers. Inquisit collects the information from the testing, which is then downloaded by the research team, again using a password-protected site.

Characterizing brain health in HIV: Understanding brain health in the overall context of living with HIV

Aim 1: To estimate the extent to which HIV-related clinical factors and patient-centered outcomes relevant to brain health and its consequences inter-relate and evolve over time.

This aim will provide a biopsychosocial analysis of the complex relationships between cognitive deficits, other impairments and symptoms, function in everyday life, and quality of life (QoL). We will trace the connections between biological variables, objective measures of cognition, and the constructs that really matter to patients (such as perceived health, which predicts longevity[22,23], and QoL-the reasons for living!). An understanding of these links is crucial for prioritizing future work, including intervention development. As described above, the framework will be the Wilson-Cleary (W-C) model. There have been only three studies[24,25,21] using the W-C model in HIV, with a restricted set of variables, and none included cognitive constructs. The advantage of this approach is that the antecedents, correlates, and consequences of brain health can be fully described, leading to a better understanding of how to optimize function, perceived health, and QoL in the presence of cognitive deficits. Our team has successfully applied this approach in a number of areas, including aging, stroke, obesity, MS, and advanced cancer [26-32].

Preliminary data collected in preparation for this proposal in 75 persons meeting the inclusion criteria planned for this project show the potential of this approach: That sample, recruited from the McGill clinic, had an average age of 47 years. Strikingly, only 44% were working. It is interesting to compare

this to a study we recently completed in multiple sclerosis (average age 42 years), where 70% were working. What are the contributors to this low rate of employment in HIV? How do cognitive deficits, whether perceived or measured, affect work and work-productivity? What is the relationship between and among these variables and perceived health and QoL? What are the modifiable factors that could be a focus of intervention? These questions, and others with similarly high potential impact, can be rigorously addressed within the platform framework. As just one example of how these comprehensive descriptive data will be applied, the link between cognitive ability and employment is likely mediated through other variables such as mood, anxiety, and fatigue. This hypothesis can be tested using the platform, and if confirmed, would form the basis for a specific multi-focal intervention. Understanding these links both at the group level and the individual level would provide a framework tailoring interventions to individuals and modifying these in the presence of cognitive concerns.

Validating better measurement tools

Aim 2. To contribute evidence for the validity of a brief brain health assessment approach combining both patient-reported and measured cognitive deficits

The first step in understanding cognitive change in HIV is to be able to measure it. As introduced above, everyday clinical experience and even the most cursory review of the literature on HAND indicates that there is an unmet need for well-validated, low burden cognitive assessment tools[33]. The clinical history alone is inadequate, as self-reported cognitive symptoms may not be predictive of objective performance[34]. Full neuropsychological assessment is the gold standard for diagnosis, and consensus recommendations on appropriate tests exist, but such tests require highly trained personnel available only in a few specialized centres[2]. Neuropsychological screening batteries are briefer, but time savings come at the expense of precision, and this approach still requires a neuropsychologist, limiting feasibility in many settings. Measurement limitations hamper research, too: Interpreting work on the underlying pathophysiology of HAND can be challenging because of variation in diagnostic rigour, sampling methods, and outcome measures. The latter is particularly an issue in intervention studies, given the limited information about the stability of cognitive indices over time, and about the meaning of changes in these indices in this population. For example, conflicting findings about whether cognition gets better[35], or worse[4],[36],[37] with HAART may relate to measurement rather than pathophysiology.

Overcoming this set of problems is a critical first step in advancing any clinical or research agenda on brain health in HIV, and consequently was the point of departure for this emerging team when we first began working together on brain health questions. This portion of the study is thus a natural extension of our team's existing work on this problem in HIV[37] , and in other, similar conditions such as prodromal Alzheimer's dementia[38]. The outcome will be a brief, adaptive, conceptually grounded approach to cognitive ability measurement that combines objective testing and patient report--a crucial knowledge translation "deliverable" of this project.

Measurement of cognitive ability is related to, but not synonymous with, diagnosis, and has distinct clinical goals. Cognitive measurement refers to the quantification of a person's performance with reference to a continuous unit of measurement along a scale representing the full spectrum of cognitive ability. Precise quantification of cognitive ability is required for comparing different treatment groups or for tracking changes in cognition in an individual patient, both goals of obvious clinical relevance in this population. Thus, the ideal measure should not only establish the diagnosis but also quantify severity. If it is to have a broad impact, it should also be free, brief, easy to administer with minimal training by any health professional, and available to clinics where HIV patients receive their care.

What are the alternatives? Pencil-and-paper tools for cognitive assessment are brief and easily administered, but fall short of the ideal in other respects. Tools such as the HIV Dementia Scale (HDS), the International HDS, and the Folstein mini-mental status examination (MMSE) are relatively insensitive to the milder cognitive signs that predominate in the HAART era. Our own work has found that this is also true of the potentially more sensitive Montreal Cognitive Assessment (MoCA) (Koski 2012). Furthermore, such scales were designed to detect, but not to *measure*, cognitive impairment: A total score is derived from summing together the scores for individual items but, because this score does not represent a continuous quantity of cognition, it is not suitable for monitoring change over time.

We propose here to use modern psychometric methods, specifically Rasch Measurement Theory, to test the hypothesis that questionnaire items capturing patient-reported cognitive complaints, and performance on various neuropsychological tests, relate to the same underlying "latent" construct – termed here cognitive ability – in such a way that the items form linearized units along a continuum from least ability to most ability. If the items fit the underlying hypothesized linear model (Rasch model), they form a measure with units that are interpretable as a quantity and which can be used in mathematical transformations, such as those to calculate change, in a valid way. Our published work using Rasch Theory, in which we combined MoCA and computerized test items to quickly estimate cognitive ability in HIV[37], and work recently completed by members of our team which added patient-reported outcome (PRO) items to these objective items, provides preliminary evidence for the hypothesis that objective cognitive measures and self-reported items do map in a hierarchical way to the underlying conceptual model. This is a novel insight with both conceptual and practical importance. First, it argues that patient report on certain questionnaire items does relate to their level of cognitive ability: what patients are telling us about their cognitive function matters, if we know what to ask and how to interpret it. Because both PRO and neuropsychological items fit together (i.e. fall within the same linear hierarchy), this portfolio of items measures the same construct. Either PRO items or a specific set of neuropsychological tests can be used alone to estimate the level of cognitive ability; combining the two adds discrimination between subjects not achieved by either alone. Once fully validated, this will have major translational implications, showing the way towards an approach to tracking cognitive ability in individual subjects (and comparing across subjects) that can be readily applied in the clinic: coarsely stratifying patients based on their responses to a few questions, allowing identification of those needing more detailed assessment with objective testing, and in every case providing an estimate of the "quantity" of cognitive ability for each individual on a common scale.

With this preliminary evidence, we will proceed with a replication of this experiment in the new sample. The minimum sample size for this type of calibration is 50 and hence even if retesting in another group of 50 is warranted (anomalous items may need to be reworked and retested), we will have a testable version of a brief adaptive measure combining objective developed very early in the cohort establishment. The result, christened B-CAM, will then be tested for sensitivity and specificity against the reference standard neuropsychological battery in a validation sample of 260 participants (see Figure 1)

The specific research steps to meet this objective are: (1) to compare the strength of the relationship between the results of the reference standard cognitive assessment and the B-CAM. Our hypothesis is that the ranking of the constructs in terms of magnitude of association will be statistically similar between the reference standard and the brief tests. The second step will be (2) to estimate the accuracy of these brief cognitive measures against reference standard neuropsychological testing.

Optimization of B-CAM and questionnaires: One of the goals of the current study is to develop brief assessment tools that can be easily used in the clinic. The final product will use an adaptive, item bank approach, developed through Rasch analysis. We plan to optimize these measures throughout the study period, by conducting interval analyses of the performance of the items that make up the measures, adding, dropping, adjusting or replacing with similar items as needed to improve overall performance. Rasch analysis allows this fine-tuning without compromising the core measure's use as a primary outcome throughout the study. This means that the exact composition of the measure may vary over time: for example, one memory test may be substituted for another, or one questionnaire item may be found to be too easy, and be replaced by one or more alternatives. This will ensure that participants do not continue to needlessly complete test items that we find are uninformative, and will support our long-term objective of providing a useful, brief cognitive measurement tool. Throughout the process, we will ensure that time required for administration of the tests is unchanged or shorter than the initial measure described here.

Reference standard: The neuropsychological battery recently developed for CIHR Canadian HIV Trials Network (CTN) studies, the CTN Neurocognitive Battery, will serve as the reference standard. This battery allows diagnosis of HAND as per the 2007 definition (Antinori 2007) by testing at least 5 cognitive domains with at least 2 tests per domain, while being as brief as possible. The tests, listed in Table 2, can be administered in under 90 minutes. The CTN Neurocognitive Battery was developed through a rigorous process that included a comprehensive literature review. In addition to diagnostic and feasibility considerations, tests were chosen to be available in both English and French with norms suitable for use in Canada. The final battery was established with expert consultation from neuropsychologists Alain Ptito, who has decades of experience with research quality neuropsychology testing in Canada in both languages, and Lucette Cysique, a leading international expert on cognition in HIV, both also key members of the present team.

RATIONALE AND CLINICAL SIGNIFICANCE

This research program strives to understand the burden of cognitive deficits, risk factors, progression, and underlying mechanisms, and on methods to streamline the cognitive evaluation process and ultimately to optimize brain health through targeted interventions. We know that brain health in HIV is complex: other medical, neurological and psychiatric co-morbidities, and aging itself, can manifest as cognitive impairment. It is crucial to untangle and manage this heterogeneity. We have chosen the term "brain health" as the entity under study in this research program to reflect the intertwining of these manifestations in this complex chronic illness. The platform will also provide a basis for gathering sample-wide data on self-management priorities, acceptability and accessibility of computer-based cognitive training, and on behavioural factors that are the target of interventions: physical activity, exercise barriers and preferences, smoking, drug use, and healthy eating behaviours. This information, along with data collected in tandem from the broader HIV community in Quebec and BC through Internet surveys and focus groups facilitated in tandem with our team's knowledge user members, will be used to define more intensive, targeted interventions to improve cognitive ability beyond what can be accomplished with basic information alone.

People with HIV cannot afford to wait for researchers to fully understand this complexity. They are facing brain health challenges today, with real meaning for their everyday function. Research in other chronic neurological disorders has provided the tools to help these people now. In particular, research on the effects of exercise, self-management and cognitive training in healthy aging and mild cognitive impairment (MCI) shows promise in improving cognitive functions that are also commonly affected in HIV[33]. The platform will provide a sampling frame for pilot studies of various interventions, and of

various substudies examining specific mechanisms in more detail. Ethics approval will be requested for these additional studies separately.

POTENTIAL RISKS AND BENEFITS

There are no risks in participating in this study. Blood sample will be taken at the same time as routine blood tests for standard of care, during this time participants may experience some slight discomfort at the site of the needle entry and a small bruise may develop.

All participants will be offered basic brain health educational materials, developed by our team, providing evidence-based information (*"Simple steps to brain health"*) through both print and Web-based delivery, in English and French. Information gained from this study will contribute to a greater understanding of neurocognition and HIV. It will allow health care professionals to make better recommendations on issues of prevention, diagnosis and treatment in general. The information will also help contribute to the development of services, which correspond more specifically to the particular health needs of HIV positive patients suffering from cognitive disorders.

Participants will have the opportunity to participate in additional studies, if they are eligible and so choose, including trials of interventions.

STUDY HYPOTHESES

This longitudinal cohort of aging HIV positive individuals will contribute to new knowledge on neurocognitive decline providing insights into the natural history and impact of cognitive symptoms and deficits, allowing us to define the heterogeneity underlying poor brain health, and for those who report good brain health at baseline, shedding light on the incidence of cognitive deficits in this aging population. This study will also allow the validation of a brief, computerized approach to measuring cognitive ability against the current reference standard, resulting in a cognitive assessment tool practicable for routine clinical monitoring of brain health. Finally, this cohort will serve as a sampling frame for intervention and mechanism-based studies that will be addressed in separate protocols.

STUDY OBJECTIVES

Primary Objective

The primary objective is to estimate the extent to which HIV-related clinical factors and patient-centered outcomes relevant to brain health and its consequences inter-relate and evolve over time using a brief cognitive ability measure (B-CAM).

Secondary Objectives

(i) To contribute evidence for the validity of a brief brain health assessment approach combining both patient-reported and measured cognitive deficits;
(ii) To estimate the accuracy of a brief cognitive ability measure (B-CAM) against standard neuropsychological testing
(iii) To contribute evidence for the feasibility, effectiveness potential, and acceptability of promising interventions for optimizing brain health; and
(iv) To explore the mechanisms underpinning longitudinal change in brain health.

STUDY DESIGN

Description

The proposed study is a prospective cohort study. We will accrue our population through consecutive sampling from five clinics: in Montreal, the Chronic Viral Illness Service at the Montreal Chest Institute, McGill University Health Centre and Clinique Médicale l'Actuel, a large primary care and HIV clinic; in Vancouver: the AIDS Research Program (at St Paul's Hospital); in Toronto, Maple Leaf Medical Clinic and, in Hamilton, Special Immunology Services Clinic.

A total of 900 participants (150-300 per clinic) will be comprehensively assessed and followed longitudinal at 9 month intervals over a 27 months period for a total of 4 assessments (5 assessments if participant is selected to have neurocognitive evaluation).

Expected Duration of Subject Participation

Participants will be expected to participate in this study for a total of 27 months.

Early Termination

Participants may revoke their consent to participate in this study at anytime.

ELIGIBILITY CRITERIA

Inclusion Criteria

- Age ≥ 35 (If necessary, we will oversample patients > 60 years old and women to ensure at least 100 of each are enrolled)
- HIV+ for at least 1 year
- Able to communicate adequately in either French or English
- Able to give written informed consent

Exclusion Criteria

- Dementia as defined by MSK-rating stage 3 or more- cognitive component only (Appendix 1)
- Concern about capacity to consent
- Life expectancy of < 3 years or other personal factor limiting the ability to participate in follow-up
- Non-HIV-related neurological disorder likely to affect cognition,
- Known active CNS opportunistic infection or hepatitis C requiring IFN treatment during the follow-up period
- Known psychotic disorder
- Current substance dependence or abuse (as per DSM-IV criteria) within the past 12 months.

CO-ENROLLMENT GUIDELINES

There are no stipulations for co-enrollment in other observational or interventional studies. Participation in other clinical studies should be documented.

TREATMENTS/ INTERVENTIONS

There are no treatments or interventions in the current study. Participants of this cohort may be asked to participate in future interventional studies; however additional consent will be required.

STUDY EVALUATIONS/ PROCEDURES

Informed Consent

Candidates for the study will be identified using the database of patients currently followed at the clinic; Director Professional Service (DPS) authorization will be requested. For those who are eligible, a form briefly describing the study will be given to them by the receptionist when they register for the regular medical visit (see attached), which they will be invited to complete and bring back to reception. On the form, they indicate whether they agree to be approached by the research assistant (RA) responsible for the study to discuss the study in more details. If the patient is interested, the RA will review the exclusion criteria with the physician. We have chosen this recruitment scenario based on previous cognition studies conducted at the clinic. These studies do not involve prescription of any medication; hence inclusion/exclusion criteria involve minimal medical decision. Patients have told us that they often have a lot of time as they wait for the doctor's appointment, but often have to leave in a hurry afterwards, limiting the time available for them to ask their questions. Once the physician has agreed to the patient's participation in the study, the subject will be asked to read and sign the approved informed consent form (ICF) (Appendix 2) prior to any assessments being performed. A brief questionnaire will be used to identify characteristics of all persons approached for recruitment to determine whether non-participation would introduce a selection bias into our study. We will be documenting age, sex, work status and cognitive status. This information will be kept anonymous and confidential.

Subject Identification Number Assignment

Subject Identification (ID) numbers will be assigned sequentially to each subject who is eligible and provides informed consent to participate in the current study by an automated web-based program. Subjects who are not eligible for the study will not be assigned a Subject ID Number. Details for assigning Subject ID Numbers will be provided in the Operations Manual. Log(s) should be completed by each site to capture all subjects who have consented and who have been assigned a subject identification number. If a patient discontinues from the study, the Subject ID Number will not be reused. The Subject ID Numbers will be used for identification of subjects in the source documentation, hand written questionnaires and laboratory samples. This will ensure that subject data and laboratory samples leaving the study sites will be identified and tracked.

Clinical Evaluations

Blood pressure, waist and hip circumference, weight, and height will be documented in Case report forms (CRFs) at each visit. Clinical charts will be reviewed and documented in CRFs for variables such as: date of HIV diagnosis, date of initiation of highly active antiretroviral therapy, CD4 count nadir, history of antiretroviral treatment and co-infections: hepatitis A, B, C; syphilis, co-morbidities: diabetes, cardiovascular disease, hypercholesterolemia, bone disease, cancers, AIDS related diagnoses and other medications. Details will be provided in the Operations Manual.

Questionnaires

Questionnaires will collect information on socio-demographic characteristics, symptom status, functional status, health perception and quality of life (Questionnaire Package, enclosed). Data collection will be carried out using a common, secure, web-based data capture system. It will take approximately 2 hours to complete the questionnaires. Participants will be given four options to complete these questionnaires:

1) ***Internet***: Participants will be asked to provide their email address once they have signed the informed consent form. The questionnaires will then be emailed to them.

2) ***Mail***: Participants will be asked to provide their address once they have signed the informed consent form. The questionnaires will then be mailed to them. The participants will be asked to return them by mail in a provided pre-addressed envelope.
3) ***At the clinic***: Participants may complete the questionnaires directly on a clinic-based computer, guided and overseen by the study research assistant as needed**.**
4) ***Over the phone***: Participants will be called at home by the RA at a time that has been mutually agreed upon, and together, they will go over the questionnaires ***while the RA*** fills in the information.

B-CAM

B-CAM will be used to assess cognition each visit. Research assistants at each site will be trained to administer these computer-based evaluations. We estimate this to take a maximum of 30 minutes to complete.

Educational Brain Health Material

Educational material on brain health (*"Simple steps to brain health"*) will be given to the participant at the initial visit (see Appendix 3.), and will be made available on the study website.

Neurocognitive Assessments

A subset of the study population (260 participants) will be selected to have a neurocognitive evaluation performed. Details on how the selection will be made will be available in the Operations Manual.
The operations manual for this battery has already been developed in collaboration with experts at CTN to ensure that it is administered in a similar way across sites. This testing (Table 2) will take place at a time that is agreed upon, either during one of the clinic visits or during a separate visit.

Cognitive Domains	**Tasks**
Memory (learning/recall)	• HVLT-R, BVMT-R
Executive Functioning	• Tower of London, Stroop, TMT-B
Attention/Working Memory	• Letter/Number Sequencing, Spatial Span
Processing Speed	• Symbol Search -WAIS IV, Digit Symbol Coding, TMT-A
Verbal/Language	• Letter Fluency (F, A, S), Category fluency
Motor	• Grooved Pegboard dominant hand, non-dominant hand
IQ estimation	• Vocabulary and Matrix Reasoning (WAIS IV)
Time of evaluation	**1h30**

Table 2: Reference Standard (CTN) Neurocognitive Battery

Laboratory Evaluations and Sample Collection

Blood samples will be obtained for clinical laboratory evaluations at each study visit as per routine clinical care- see attached list. Subjects should be fasting for at least 8 hours prior to blood work. All clinical laboratory evaluations will be performed at site local laboratories as per local standards of care. When possible, laboratory results will be transferred directly to the main web-based database by the research assistant. If this is not possible at the participating sites, CRF will be available for the sites to transcribe the results.

Stored Research Samples

At baseline and 27 month visits research blood samples are to be collected/processed, and clearly labeled. Subjects should be fasting for at least 8 hours prior to blood work. Samples will be shipped to the Immunodeficiency Laboratory in Montreal depending on site availability for sample storage. Clinical laboratory evaluations will be performed at a local private laboratory and will include tests that

are not performed as per standard of care and that are relevant to the study. Detailed processing, storage, and shipping instructions for each specimen will be provided in a separate laboratory manual. The Principal Investigators will have access to the specimens and data, whereas the research assistants and the study coordinator will only have access to data. When possible, laboratory results will be transferred directly to the main web-based database by the research assistant. If this is not possible at the participating sites, CRF will be available for the sites to transcribe the results. Subjects may decide at any point not to have their specimens stored. In this case, the principal investigator will destroy all known remaining specimens and report what was done to both the subject and to the IRB/REB. The samples will not be made available to any commercial enterprise. Stored samples will be identified only by a code number and will be destroyed after 15 years.

Serum Collection

At baseline and 27 months, blood will be collected in a 1x7.5mL yellow top SST Vacutainer. Study personnel will collect as many 500uL aliquots of serum into pre-labeled 1.5 mL cryovials (approximately 5 cryovials) as possible. Detailed instructions for the collection, storage and shipment of the serum samples will be provided in the operations manual. Cryovials will be frozen at -80^0 C in well-labeled boxes and collection and storage will be documented as outlined in the laboratory manual.

Plasma Collection

At baseline and 27 months, blood will be collected in a 2 x 10 mL lavender top EDTA Vacutainer. Study personnel will collect 10 x 1000uL aliquots of plasma into pre-labeled 1.5 mL cryovials. Cryovials will be frozen at -80 ^{0}C in well-labeled boxes and collection and storage will be documented as outlined in the laboratory manual.

PBMC Collection

ONLY for Montreal Sites:
Blood will be collected in a 4 x 10 mL lavender top EDTA Vacutainer and shipped to the Immunodeficiency Laboratory within 4 hours of collection. Detailed instructions for PBMC preparation, separation, counting and freezing will be provided in a separate laboratory manual. PBMC samples will be stored at -80 ^{0}C for 24 hours. The samples will then be transferred to a liquid nitrogen tank for long-term storage (in vapour phase) and collection and storage will be documented as outlined in the operations manual. This will be done once, at the baseline visit.

Telomerase Assay

At baseline and 27 months, a pre-labeled 5 mL plastic EDTA coated tube of blood will be collected and stored at -80 ^{0}C.

DNA sample

If participants agree to participate in the optional DNA analysis, we will ask them to provide 1 saliva sample. Consent to DNA testing will be mentioned specifically on the Informed Consent document.

Urine toxicology test

At one point in time, a minimum of 30 ml of urine will be collected in a specimen collection container.

Transportation of Laboratory Samples

Details for sample shipment will be provided in the laboratory manual. All shipments will be prepared by qualified individuals ensuring that all shipments are packed and shipped according to IATA regulations for the shipment of infectious and dangerous goods. All samples will be clearly labeled and

must be accompanied with a copy of a shipment list. Prior to shipment of samples, the sites will notify the central laboratory regarding the date of shipment to ensure receipt of the shipment.

STUDY VISITS

Screening for Subjects

The screening visit is anticipated to require 1 hour of the subject's time. During this visit the following will take place (this visit can be performed on the same day as the baseline visit):

- Informed Consent
- Review of Eligibility Criteria
- Assign Subject ID Number

Baseline Visit for Subjects

This visit may occur at the same time as the screening visit. This visit is anticipated to require 4 hours of the subject's time (this includes 2 hours the participant may spend at home). The following events will take place.

- Chart review (patient medical history)
- Questionnaire
- B-CAM
- Basic Brain Health educational materials will be provided to participants
- Standard of Care blood tests
- Research blood (these samples will be shipped to the central laboratory at the Montreal Chest Institute to be processed)
- Saliva samples if determined by central coordination
- Urine toxicology test if determined by central coordination
- Anthropomorphic measures

Follow-up Visit for Subjects

Study visits (9, 18 and 27 months)**:**

These visits may occur within 6 weeks of each scheduled visit. Each visit is anticipated to require 3 hours of the subject's time (this includes 2 hours the participant may spend at home). The following events will take place.

- Chart review (patient medical history since their last visit)
- B-CAM
- Questionnaire
- Standard of Care blood tests (these results will be extracted from patients' charts)
- Research blood samples (27 months only, these samples will be shipped to the central laboratory at the Montreal Chest Institute to be processed)
- Anthropomorphic measures

- Saliva samples if determined by central coordination
- Urine toxicology test if determined by central coordination

STUDY MANAGEMENT

Local Coordination

Each collaborating investigator will be responsible for recruiting study personnel, obtaining local REB/IRB approval, ensuring local clinic staff are informed about the study, and supervising local study activities. The study personnel at the site will be responsible for: identifying participants; obtaining informed consent; conducting study visits; ensuring subjects have regular follow-up; encouraging attendance at visits; telephoning subjects if visits are missed; and collecting subject data. A study manual will outline methods for questionnaire completion and record management. Personnel will also be trained on study procedures prior to and during the study. The informed consent forms and study questionnaires will be translated into French for use in Quebec.

Central Coordination

A Study Manager will coordinate the day-to-day management of the study. A computerized study database will be created by data management committee and managed by Dr. Nancy Mayo in Montreal.

Communication

Regular investigator meetings will be planned by teleconference to keep study personnel informed of study progress, and to encourage ongoing recruitment.

DETAILS OF STATISTICAL ANALYSIS

Analysis and Sample Size: Traditional analysis of variance or regression type statistical approaches will not be adequate to link the measured constructs together. Indeed, the existing literature on these questions may be misleading because of the pitfalls of addressing this kind of data complexity with traditional analytic methods[39]. Instead, our approach will be to use methods of causal modeling, i.e. Structural Equation Modeling (SEM). This method is one of a family of related, sophisticated, multivariate, statistical procedures for testing how well theoretical models conform to the data. SEM consists of two basic elements: a measurement model, analyzed by factor analysis, and a structural model, using path analysis. SEM uses latent variables to represent the constructs of interest, recognizing that complex constructs are not adequately represented by any one single measure, and thus the commonality between related measures is a better representation[40]. This method will permit the direct and indirect effects of cognitive deficits to be situated within the broader context of HIV morbidity, co-morbidities and life impact of HIV infection.

Sample size for SEM is large: optimally 15 to 20 people per parameter estimated. The number of parameters estimated in a complex model can be substantial (approximately 3 per included latent variable) therefore sample sizes in the range of 400 to 600 would be needed for the W-C model. Given the focus on cognition, it would be informative to identify if the structure and relationships between and among variables differ in the presence of cognitive deficits. As we are expecting about 40% to have some cognitive deficit (measured or reported), a sample size of 900 would yield about 360 persons for an SEM model. We would also like to test the effect of age on these relationships, which will be possible with our recruitment plan that will ensure a minimum of 100 persons 60 years and older. This model can be fit longitudinally, providing the opportunity to understand how changes in key constructs affect health and function over time. In addition, the platform will serve as a sampling

frame for a series of focused studies in selected sub-groups, addressing specific pathophysiological and clinical questions. These are organized around four themes: understanding how aging interacts with HIV to affect brain health trajectory, understanding the neural, viral and inflammatory mechanisms supporting resilience and recovery of cognitive ability, including the role of HAART CNS penetration, and understanding the mechanisms underlying isolated subjective cognitive complaints in the context of depression. The platform will also serve as the basis for longitudinal follow-up of the cohort to address heterogeneity of the HIV population in terms of evolution over time of cognitive deficits, and co-evolution of cognitive deficits with antecedent variables, correlates and consequences. A better understanding of the natural history of cognitive deficits (measured and self-reported), particularly in relation to aging and aging-associated co-morbidities, will be vital for counseling patients and targeting diagnostic and intervention resources in the clinic. Here we will use a form of latent trajectory analysis (group-based trajectory analysis; GBTA)[41]. We have designed this study to optimize the characterization of longitudinal change: four time points allow non-linear trajectories to be evaluated. Our group has expertise in this methodology, including its application to characterize evolution of cognitive impairment over time in an elderly population[42 42], and apathy in a stroke population[43 43]. The sample sizes projected for this study should yield up to 5 to 7 distinct trajectories[44], providing a detailed view of the heterogeneity of longitudinal change and of factors contributing to trajectory of change. Additional multivariate approaches may be warranted, such as mixed models, to assess the impact of key variables on longitudinal change in brain health.

To formally estimate the sensitivity and specificity of B-CAM, we will use the classical method of Begg and Greens [45], which assesses diagnostic tests when there are different verification probabilities. Because the new measure, B-CAM, is mapped to a standard normal distribution (on a logit scale), it is possible to use the distribution to identify a cut-point for further testing. Validation will take place on the first 500 consecutive persons enrolled. We will verify 100% of the persons who score below the mean on B-CAM and a random sample of 20% of those who score above this level, stratified by SD. The sample size for this estimation is based on the formula provided by Begg and Greens for sensitivity, specificity and corresponding 95% confidence intervals (CI). Under the assumption that approximately 40% of people will score in a range indicative of cognitive deficit on B-CAM, 90% of those who test positive for cognitive deficit on B-CAM will be verified by standard neuropsychological testing, and 90% of those who test negative will also be verified negative, we propose to test the accuracy of B-CAM on a sample of 200 persons (Fig. 1). We intend to test 100% of all those with B-CAM evidence of deficit (500 * 0.4 = 200) plus 20% of the remainder (0.2 * 300 =60). With this verification strategy, and under the assumptions above, the estimated sensitivity would be 0.86 (95% CI: 0.73 to 0.93). The corresponding values for specificity are 0.93 (95% CI: 0.89 to 0.96). Even if the lower bound of the 95% CI was observed in a given clinical setting, the information gained would be clinically relevant (particularly given its ease of acquisition) given that the clinician interpreting B-CAM results would have additional clinical information, and could always repeat B-CAM a few months later to clarify whether apparent deficits persist or worsen in uncertain cases. We will also estimate the effect of covariate status (age, co-infection with Hepatitis C, history of drug use, recent immigrant, or low education) on sensitivity and specificity.

Correlation (ρ)	95% CI
0.7	0.637 – 0.754
0.6	0.521 – 0.668
0.5	0.409 – 0.581
0.4	0.299 – 0.492
0.3	0.192 - 0. 401

Additional evidence for the validity of B-CAM will come from the strength of the correlation with scores on B-CAM to scores on other measures included in the platform in comparison to the correlations between neuropsychological test results and platform measures. Correlation coefficients

can be qualitatively compared using the width of the confidence interval. With a sample size of 260 evaluated on both B-CAM and the reference standard neuropsychological battery, the width of the 95% CI around a given correlation (ρ) is depends on the magnitude of ρ as shown in the insert (right). Thus, if the correlation with our measure of depression and reference standard neuropsychological test results is 0.7, we will conclude B-CAM shows the same degree of validity as the reference standard if the correlation is within the 95% confidence band of 0.63 and 0.75 http://vassarstats.net/rho.html.

QUALITY CONTROL AND QUALITY ASSURANCE

Data Collection and Quality Assurance

Whenever possible, data will be transferred electronically from the source to the study database. Source documentation will not be verified by an on-site monitor visit during the study. The study manager will be responsible for central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance. It is the responsibility of the Principal Investigator to assure the quality of computerized data for this study.

ETHICS/ PROTECTION OF HUMAN SUBJECTS

ICH Guidance E6: Good Clinical Practice: Consolidating Guideline/ Declaration of Helsinki

The conduct of this study will conform to the International Conference for Harmonization and Good Clinical Practice (ICH-GCP) regulations and guidelines and the current revision of the Declaration of Helsinki.

Study participants may have cognitive impairment, and so constitute a potentially vulnerable population. Particular attention will be paid to the informed consent process in light of this potential vulnerability, keeping in mind the non-invasive, low risk nature of this study. The patient's physician will be asked if he/she has any doubts about the patient's capacity to consent. In addition, if there is evidence during the consent process that the patient does not understand the consent document, cannot paraphrase the purpose, risks or benefits of the study after these have been explained, cannot articulate a choice, or does not appreciate that the study is for research purposes rather than part of their medical care, the patient will be excluded from the study. The consent process will emphasize that participation, refusal, or withdrawal from the study has no bearing on the patient's on-going clinical care.

It should be emphasized that there is no physical risk to participation in this study, beyond boredom or fatigue in completing the testing. Prior to the testing, patients are informed that it is fully expected that they will fail on some items as the testing session is built in this way. The person administering the testing will have the necessary training to sensitively handle distress that may arise during testing. Frequent breaks will be offered to mitigate the fatigue that may arise. One immediate benefit to the participants is the access to the educational material on Brain Health. In addition, interventional studies are planned, for which participants may be eligible; separate consent will be obtained for these later trials.

Research Ethics Board/ Institutional Review Board

A copy of the protocol (including protocol amendments), all versions of the informed consents, other information to be completed by subjects such as questionnaires, and any proposed advertising/ recruitment materials must be reviewed and approved by the REB/IRB of each participating centre prior to implementation of the study. The site investigator will be responsible for obtaining REB/IRB approval of the annual Continuing Review throughout the duration of the study.

Informed Consent Process

All subjects will be given detailed oral and written information about the study. Consent forms describing in detail the study procedures, anticipated benefits and potential risks will be given to each participant and written documentation of informed consent is required prior to starting the study. Subjects must voluntarily sign and date an informed consent document that has been approved by a participating centre's REB/IRB prior to any procedures being done specifically for the trial. Consent for DNA testing will be included in a separate section of the ICF. Use of certain questionnaires is conditional upon sharing of denominalized information with the copyright holder: consent for sharing this information will also be specifically obtained. Each subject should have sufficient opportunity to discuss the study and consider the information in the consent process prior to agreeing to participate. Subjects may withdraw consent at any time during the course of the trial. The informed consent will be signed and dated by the subject, the person who conducted the informed consent discussion and the investigator. The original signed informed consent form will be retained in the subject's study files and a copy will be provided to the subject.

Participant Confidentiality

All subject related information including the questionnaires, laboratory samples, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject, and a subject letter code. All computerized databases will identify subjects by numeric codes only, and will be password protected. Upon request, clinical information may be reviewed by or released to auditors, CIHR or regulatory agencies.

Record Retention

Data and study documents at all sites will be stored securely for 25 years, after which they will be destroyed in keeping with the privacy and confidentiality regulations and guidelines. Samples collected and sent to the central laboratory will be retained for 15 years, after which they will be destroyed.

DATA MANAGEMENT RESPONSIBILITIES

Instructions concerning the recording of study data on case report forms will be provided by the Principal Investigator. Each study site is responsible for submitting the data in a timely fashion. It is the responsibility of the Principal Investigator to assure the quality of computerized data for this study. This role extends from protocol development to generation of the final study databases.

Protocol Violations and Deviations

Requested minor protocol exemptions may be considered on a case-by-case basis and documented. Protocol violations or deviations must be reported to the Principal Investigator. Protocol exemptions, violations, and deviations will be logged.

Study Conduct and Monitoring

Data will be monitored by the study manager upon CRF and questionnaire completion. Source documentation will not be verified by an on-site monitor visit during the study. It is the responsibility of the Principal Investigator to assure the quality of computerized data for this study.

Source Documents and Access to Source Data Documents

Each participating site must maintain appropriate medical and research records for this study and regulatory/ institutional requirements for the protection of confidentiality of study subjects. The Principal Investigator is responsible for assuring that the data collected are complete, accurate, and

recorded in a timely manner. Clear and detailed instruction explaining CRF completion will be included in the study Operations Manual.

DISCLOSURE AND PUBLICATION POLICY

Publication of the final study report is planned. Dr. Lesley Fellows and Dr. Marie-Josée Brouillette will determine authorship for each manuscript based on contributions to the study design, study execution, and manuscript completion. No author will be included without prior authorization but the intention is to be broadly inclusive of all study investigators who make active contributions as outlined by The ICJME criteria for authorship (i.e. Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3).

COMPUTERIZED COGNITIVE TRAINING INTERVENTIONAL SUB-STUDY

Background information

Cognitive deficits in HIV may reflect degraded brain network functioning, due to a combination of brain health insults: some generic (aging), some HIV-specific (inflammation, diffuse demyelination and inherent vulnerability that varies across individuals). Consistent with this hypothesis, the cognitive domains most affected are those that rely on extended networks (e.g. attention and executive functions relying on fronto-parietal and fronto-striatal circuits), exquisite timing (psychomotor function), or both. These network-based cognitive functions are vulnerable, but they are also resilient: there is a high degree of learning-dependent plasticity in networks involving the frontal lobes [46-49]. This argues that the cognitive deficits in HIV may be amenable to remediation through cognitive training, and suggests mechanisms by which this might occur. There are many forms of cognitive rehabilitation; approaches that take advantage of advances in our understanding of the mechanisms of neuroplasticity and the neural systems supporting human cognition are likely to be highest yield[50,51]. In this sub-study, we will make use of Plasticity-based Adaptive Cognitive Remediation (PACR), a powerful method for harnessing this plastic potential. Conceptually, PACR applies well-understood techniques derived from brain plasticity and implicit/procedural/perceptual learning to improve the speed and accuracy of information processing, with exercises that are designed to drive generalized improvements. Simultaneously, these exercises heavily engage neuromodulatory systems to re-establish their normal control over learning and memory. As an individual restores these degraded abilities through intensive procedural learning, the encoding of naturalistic information significantly improves, and all resulting declarative memory and cognitive functions based on the quality of that incoming information necessarily improve as well, leading to improvement that generalizes beyond the trained tasks. Multiple randomized controlled studies have now demonstrated that PACR improves cognitive and functional abilities in patient populations with cognitive dysfunction similar in type and magnitude to patients with cognitive deficits due to HIV[48,50,52-54].

PACR cognitive training program

PACR runs in a web browser on any Internet connected computer and is implemented in an engaging game-like format. The training program is administered online: the participant opens a standard web browser on a broadband-connected computer and goes to the PACR study web site (following a link from the Brain Health project's website). The participant then logs into the PACR (using a study-provided screen name that contains no personally identifiable information). A game-like experience begins, where the participant is encouraged to earn points and in-game rewards to advance. To do so, the participant selects one of the cognitive exercises scheduled for the day, and performs that exercise for fifteen minutes. Participants perform tens to hundreds of trials over the course of the fifteen-minute session, with each trial providing auditory and visual feedback to indicate if the trial was performed correctly or incorrectly. The training is individually tailored to maximize its effectiveness. Summary screens including game metrics (points, levels) and exercise metrics (usage, progress) are shown to the participant at the end of each session. The scheduling mechanism ensures that a patient progresses through the exercises in a defined order, generally moving from more simple (early sensory processing) exercises to more complex (multimodal, cognitive control) exercises over the course of the 8 week experience. At any point in time, the participant only has access to a subset (typically six) of these exercises, four of which are performed per day.

Each exercise has specific criteria for completion, and after those criteria are met the exercise is removed from the active set and the next exercise added. This mechanism ensures both ongoing novelty and engagement for the participant, and that the participant progresses smoothly through the complete set of exercises over the program use period.

Free access will be provided to the PACR program, with a tailored cognitive training program available in both French and English, specifically targeting domains and mechanisms that are most affected in HIV.
The treatment goal will be use of the assigned program in 30 minute sessions, five sessions per week, for eight weeks after randomization; program use will be any mix of at home (or community Internet resource) or in-clinic sessions.

Training data management

All usage and progress data are encrypted and transmitted to a central server. No personally identifiable information, including Internet protocol addresses, is stored on the server. On the server, the data are available for review by the Site Trainer, Study Coordinator, and Site PI through a secure web portal. A given site's staff can only view data from participants at that site. The Site Trainer will use the secure web portal to regularly check on usage and progress of each active participant to customize their weekly phone discussions to provide helpful guidance and coaching.

CLINICAL SIGNIFICANCE

The results of this study are expected to be pivotal in generating data to create an optimal training program aimed at stabilizing or improving brain function in HIV infected individuals experiencing cognitive decline. We anticipate that the results from this preliminary study will motivate a larger scale trial.

POTENTIAL RISKS AND BENEFITS

There are no foreseeable risks associated with participating in the study. After a routine follow-up visit for the core platform, all participants will be asked to attend an information and training session. Additionally, about 4 months after their enrolment in this sub-study, all participants will undergo one additional B-CAM test session lasting no more than 1 hour. Participants will receive compensation for these two extra visits to offset their travel expenses, time and inconvenience ($20.00 for the training session and $40.00 for the additional B-CAM test session).

STUDY HYPOTHESIS

Eight weeks of cognitive training (PACR) is feasible and acceptable for people with mild cognitive difficulties related to HIV infection, and will lead to better cognitive performance compared to education on general strategies to improve brain health.

STUDY OBJECTIVES

1. To determine whether PACR is associated with a higher frequency of cognitive improvement (measured by the B-CAM) compared to education on general brain health strategies.

2. To assess the feasibility and acceptability of the planned PACR training strategy in people with HIV and cognitive complaints, as measured by number of sessions completed and performance on the training exercises over time.

STUDY DESIGN

Description

A subset of 65 HIV+ individuals with both cognitive symptoms and objective cognitive impairment will be randomly drawn from the main study population. The study will be piloted in five individuals, to allow optimization and refinement of study processes and procedures. After having completed a

routine study visit, participants will be asked to attend an extra session to review the information provided previously, regarding ways to improve their brain health. They will be encouraged to choose one area of their brain health to work on and will be helped to find ways to achieve a brain health goal. At this information session, participants will be randomly assigned to one of two cognitive training groups of thirty participants each. One of the groups will start the training immediately (immediate training group), whereas the other group will start the training at a later point in time (delayed training group), after having worked on achieving a brain health goal.
Before starting the PACR training, participants in both groups will be administered the B-CAM, as well as, some additional cognitive testing. Specific instructions on how to access the training program from a personal computer will also be provided.
After the completion of the PACR training, all participants will return for an in-clinic post-intervention assessment, where they will repeat the B-CAM along with the aforementioned additional cognitive testing. All participants will be given the option of continuing training on the PACR program for as long as they wish, without having to come in for any further testing.

Expected duration of subject participation
Participants randomized to the intervention will be expected to undergo the computer based PACR training in 30 minute sessions, five sessions per week, for a total of eight weeks.

Early termination
Participants may revoke their consent to participate in this study at any time

ELIGIBILITY CRITERIA
Inclusion criteria
- Evidence of mild cognitive deficits (B-CAM $\leq$ 1.5)
- Able to have convenient daily access to the Internet
- Stable medical condition
- Have been on a stable HAART regimen for > 6 months
- Have not had a change in medications that could potentially interfere with cognition in the past 4 months.

Exclusion criteria
- Past history of CNS opportunistic infection or stroke
- Current substance dependence or abuse (as per DSM-IV criteria) within the past 12 months.

TREATMENTS
There are no pharmacological treatments involved in the current study.

STUDY EVALUATIONS/PROCEDURES

Informed Consent
The subject will be asked to read and sign the approved informed consent form prior to any assessments being performed. Sufficient opportunity will be given to discuss the study and consider the information in the consent process prior to agreeing to participate. The original signed informed consent form will be retained in the subject's study files and a copy will be provided to the subject.

Subject Identification Number Assignment

Subject Identification (ID) numbers assigned for the core platform will be used for this sub-study.

DETAILS OF STATISTICAL ANALYSIS

Analysis and sample size estimation

Basic descriptive statistics will be used to characterize the sample, and to assess the feasibility and acceptability of the PACR judged by the number of sessions completed, and the presence of improvement in training performance over the eight week period. B-CAM scores will be compared between immediate and delayed training groups. This latter group will serve as a control for the immediate training group. Both groups will be assembled each with a sample size of 30 participants. The outcome will be responder status (defined as improvement of >0.5 logits) on the B-CAM. . With the assumption that the outcome is drawn from a binomial distribution with an expected probability of response of 10% (n=3) with no intervention, 30 subjects in the intervention group will allow detection of a positive response at $P<0.05$ if 7 or more persons respond. The observed responses in both groups will provide more accurate estimates to plan for a scale up of this work to a full trial. An exploratory analysis will evaluate response in only those who completed at least 60% of the training sessions, recognizing that power here will be reduced, but the information nonetheless important.

Participants from both groups will also be compared to all those eligible for randomization to this intervention in the platform as a whole. Generalized estimating equations (GEE) will be applied as a secondary, more general approach here that permits other time points to be modeled, and consideration of other outcomes. This accommodates either binary (responder status) or continuous (scores on cognitive tests) outcomes. This analysis uses a regression model, but clustering of outcomes within time is controlled. For binary outcomes, the effect of group (immediate, delayed or never trained) is expressed as an odds ratio; for continuous outcomes the parameter is an effect size equivalent to an adjusted paired-t-test. An interaction term tests whether the effect differed by group (i.e. was larger in any trained groups vs. the never trained group, as hypothesized).

Additional analyses will be used to explain changes in B-CAM score as a function of changes expected from the intervention. As the intervention cohort is small, we will use concordance parameters, rather than a regression model, to quantify the degree to which changes in hypothesized mechanisms by which the interventions operate are concordant (at the individual level) with changes in the outcomes (cognitive ability).

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APPENDIX

Appendix 1. MSK clinical staging system for the AIDS dementia complex- cognitive component

MSK clinical staging system for the AIDS dementia complex- cognitive component	
ADC stage	Characteristics
0 (normal)	Normal
0.5 (equivocal)	Absent, minimal, or equivocal symptoms, without impairment of work or capacity to perform activities of daily living (ADL)
1 (mild)	Able to perform all but the more demanding aspects of work and ADL, but with unequivocal evidence of intellectual or motor impairment, which may include impaired performance on neuropsychological testing
2 (moderate)	Able to perform basic activities of self-care but cannot work or maintain the more demanding ADL
3 (severe)	Major intellectual incapacity—cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output
4 (end stage)	Nearly vegetative, intellectual and social comprehension and output are at a rudimentary level, nearly or absolutely mute

Adapted from Price and Brew, The AIDS dementia complex. *J Infect Dis* 1988;158:1079-1083. University of Chicago Press 1988.

Appendix 2. Informed Consent Form Core Platform

INFORMATION AND CONSENT FORM

Title:	**Understanding and Optimizing Brain Health in HIV Now**
Principal Investigators:	**Dr. Lesley Fellows & Dr. Marie-Josée Brouillette**
Study Site:	**Montreal Chest Institute (MUHC)**
Sponsor:	**McGill University**
	Canadian Institute of Health Research (CIHR)

INTRODUCTION

You are asked to take part in this study because you are over the age of 35 and have been HIV positive for a least a year.

Before deciding to participate in the study, you should clearly understand its requirements, risks and benefits. This document provides information about the study, and it may contain words you do not fully understand. Please read it carefully and ask the study staff any questions you may have. They will discuss the study with you in detail. You may take this form with you and discuss the study with anyone else before making your decision. If you decide to participate, you will be asked to sign this form and a copy will be given to you.

BACKGROUND

In Canada, the effects of Human Immunodeficiency Virus (HIV) infection on brain health are unknown. Studies from other countries report high rates of depression and problems with memory, concentration or problem solving (cognition). The main component of this study aims to better understand how HIV affects brain health in different people, and how this impacts people's lives. In a group of 900 people with HIV across Canada we will assess several factors that are known to potentially impact brain health. Following the initial evaluation, participants will be followed every 9 months, for 3 additional assessments (total duration of 27 months, 4 assessments) to help us understand how difficulties with mood and cognition develop over time and their impact on every day functioning. Participants will also be eligible for pilot studies of promising interventions aimed at improving brain health.

PURPOSE OF THE STUDY

The purpose of this study is to understand how the Human Immunodeficiency Virus (HIV) affects the brain over time and how this impacts everyday activities. A total of 900 people across Canada will be asked to participate in this study.

STUDY PROCEDURES

The study will last 27 months and will involve 4 clinic visits (every 9 months) that can occur at the same time as your regular scheduled doctor's visits.

If you agree to take part in this study, your participation in the study involves the following: you will be asked to fill out several questionnaires evaluating various factors that can affect brain health; and assessing brain health itself (mood and cognition). We will measure cognition with a computerized test. In addition, blood, saliva and urine samples will be taken and some basic clinical measurements

will be performed. The blood samples that are not part of your routine medical care will be taken at the initial visit and at your 27 month study visit. You will be required to fast (nothing to eat or drink, except water) for at least 8 hours prior to the blood test. Every 9 months, we will also collect information from routine blood tests done for your HIV care, but you will also be asked to come in fasting for those visits.

You will not be required to take any special drugs as part of the study. You will receive a document on "8 simple steps of how to improve your brain health" to give you information about what you can do now to improve your brain health.

In addition, at one time point to be determined by the central coordination of the study,

- A saliva sample will be collected once at random between your first and last visit and will be used to study differences in people's DNA and evaluate if there is a genetic component to understanding how HIV affects brain health (*optional- see separate consent*)
- A urine toxicology test to look for the presence of street drugs will be performed once, at random between your first and last visit. This test will be used to validate your responses to questions related to the usage of 'hard drugs'.

Routine bloods that are part of your medical care will be drawn as usual.

At each visit the following assessments will occur:

	Assessment	**Details**	**Purpose**	**Time**
I	Cognition	This will be done with a computer-based program with the help of the research assistant.	Assess your memory, concentration, attention	30 mins
II	Research Samples (a)	30 mL (6 tsp) of blood at the sametime as your routine blood tests Montreal sites only: an additional 40 mL (8 tsp) will be collected once at baseline only.	-Evaluate biological, immunological, virological and pharmacologic functions related to HIV and cognition	5 mins
		DNA Sample; saliva sample (*optional*)	Evaluate if there is a genetic component to understanding how HIV affects cognition	2 mins
		The samples will not be made available to any commercial enterprise. These will be identified only by a code number and will be destroyed after 15 years.		
III	Toxicology test	Urine toxicology test	To detect the presence of street drugs in the body	5 mins
		The urine toxicology test is only for collecting information. The results will not be made available to anyone beyond the research staff.		
IV	Clinical	Measure your weight,	Evaluate the current state of	5 mins

	measurements	height, blood pressure, and waist circumference	your health	
V	Questionnaires	Series of questions to be answered by you	Questionnaires will assess the following aspects of your everyday life, including education and work, smoking, alcohol and drug use, cognition, vitality, stress, quality of life, illness/health perception, social support, self efficacy, HIV symptoms, depression and anxiety, physical activity, sleep	2 hours

Since the questionnaires are time consuming, you will be given several options to complete them. These include: completing them on paper; on a computer (on a secure server), at the clinic or another location of your choice (such as home); or over the phone with the research assistant, at a time that has been agreed upon. It is important that no other person answers any of the questions on these questionnaires for you. Depending on the option that you chose, you may be asked to provide your e-mail or mailing address so we can send you the questionnaires.

The total time for each visit is about 3-4 hours. If you decide to complete the questionnaires outside the clinic, the time at the clinic would be 1-2 hours, and 2 additional hours at a later time.

Your responses to these questions will only be viewed by study personnel, and not by anyone involved in your clinical care.

You may be asked to have a full neuropsychological evaluation during a separate session. This evaluation lasts between 1.5 and 4 hours, depending on how difficult the tasks are for you and whether you need time for a break. This is optional.

We will also access your personal data stored in your medical records for information like your blood results, date of HIV diagnosis, treatment history, and medical conditions other than HIV. This information would confirm medical diagnosis and medications.

Use of certain questionnaires that are part of the study require that we send the information obtained during the study to the makers of the questionnaire. The information is shared with them only after all information that could identify you has been completely removed.

RISKS

When a blood sample is taken you may have some slight discomfort at the site of the needle entry and a small bruise may develop.

POTENTIAL BENEFITS

All participants will receive a document on "8 simple steps of how to improve your brain health" to give you information about what you can do now to improve your brain health. In addition, you may

be asked to participate in an intervention study aimed at improving different aspects of brain health. With your permission, we would contact you to provide you with information about the intervention studies to which you are eligible, and ask you to participate. A separate informed consent would then be signed.

In addition, the information collected may help to gain a better understanding of brain health in people living with HIV and develop treatment interventions.

COSTS

You will not be paid for taking part in this study. However, you will be compensated for your travel and childcare up to a maximum of $40.00 per visit if you decide to complete the questionnaires at the clinic. If you decide to complete the questionnaires outside the clinic, you will be reimbursed $20.00 at the time of your visit and $20.00 after we have received the completed questionnaires.

INDEMNIFICATION/COMPENSATION IN CASE OF INJURY

If you should suffer any injury following your participation in the research project, you will receive the appropriate care and services for your medical condition without any charge to you.

By accepting to participate in this project, you are not waiving any of your legal rights nor discharging the researchers or the institution of their civil and professional responsibility.

CONFIDENTIALITY

The team of researchers of the Montreal Chest Institute will consult your medical files to take notes of the relevant data to this research project. This may include your name, address, phone number, health plan number, date of birth, medical history, and medical-related information, during your participation in this study.

All information collected for the study will be kept strictly confidential. It will not be included in your medical chart. Should any clinical results be of importance for your medical care, those results will be provided to your physician. Your name will be coded and the code list will be locked in a filing cabinet in the investigator's office at the Montreal Chest Institute with limited access. Data will be stored on a password-protected computer and kept for a period of 25 years and subsequently discarded following the completion of this study. The computer system is operated by a Montreal based third party who will host the data in the province of Québec.

The results from this research study may be published and other physicians participating in this research study may have access to your records related to this research study; however, your identity will not be revealed in the combined results.

In order to verify the research study data, monitors or Quality Assurance Officers from the McGill University Health Centre (MUHC) Research Ethics Board may review these records.
By signing this consent form, you give us permission to release information regarding your participation in this study to these entities and to the service provider where data will be hosted. Your confidentiality will be protected to the extent permitted by applicable laws and regulations in the Province of Québec.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is entirely voluntary, and if you refuse, your medical care and treatment will in no way be affected. If you choose to participate, you may change your mind and withdraw at any time. Again, this will not affect the medical care you receive in any way.

If you no longer wish to share your personal health information, you may cancel your permission at any time by writing to the study doctor. If you cancel your permission during the study, no new personal health information will be collected, and the data gathered to that point will continue to be used to evaluate the study results. However, you will be withdrawn from the study since the data required to complete the study could no longer be collected.

The principal clinical investigators and/or the MUHC Research Ethics Board are entitled to terminate the study at any time without your consent. If this is the case, you will be given a full explanation.

STORAGE AND SAFEKEEPING OF BLOOD AND DNA SAMPLES

As part of this study, we will be collecting and storing blood samples in order to evaluate biological, immunological, virological and pharmacologic functions related to HIV and brain health. As well, as an optional part of this study, we will be collecting DNA samples (saliva) in order to evaluate if there is a genetic component to understanding how HIV affects cognition (see separate consent).

If you agree to participate in this study, your saliva and blood samples will be stored for up to 15 years after the end of the study. The samples will be stored at the Chronic Viral Illness Service of the Montreal Chest Institute, 3650 rue St. Urbain, Montreal, Quebec H2X 2P4.

Should additional testing be required on your samples, the research team would seek written approval from the MUHC Research Ethics Board to do so.

We will protect the confidentiality of your samples. Any personal identification will be coded, upon the assignment of a unique identifier. Scientists working on the sample will only be able to identify a sample by its assigned number but will not know who you are. This unique identifier will be used to store your sample and any corresponding data until the final study report has been written

FUNDING OF THIS RESEARCH PROGRAM

The Canadian Institute of Health Research is providing infrastructure support for the conduct of this research. The study is being conducted by Dr. Marie-Josée Brouillette from the McGill University Health Centre. The study doctor is not being paid for including you and looking after you during your participation in this study.

CONTROL OF THE ETHICAL ASPECTS OF THE RESEARCH PROJECT

The Research Ethics Board of the MUHC has reviewed this research project and ensures its follow-up. In addition, it will first approve any review and amendment made to the information/consent form and to the study protocol.

QUALITY ASSURANCE PROGRAM

The MUHC implemented a Quality Assurance Program that includes active continuing review of projects (on site visits) conducted within our establishment. Therefore, it must be noted that all human subject research conducted at the MUHC or elsewhere by its staff, is subject to MUHC Routine and Directed Quality Improvement Visits.

QUESTIONS

If you have questions concerning matters related to this research, you may contact **Dr. Marie-Josée Brouillette** at **(514) 934-1934.**

If you have questions about your rights as a research subject and wish to discuss them with someone not connected to the study, you may contact the **Ombudsman of the McGill University Health Centre** at **(514) 934-1934 ext. 35655.**

If you believe that you have been injured as a result of participating in this study, you may contact the **Director of Professional Services** at **(514) 934-1934, ext. 48087.**

Title: **Understanding and Optimizing Brain Health in HIV Now**
Sponsor: **McGill University**
Canadian Institute of Health Research (CIHR)
Principal Investigators: **Dr. Lesley Fellows & Dr. Marie-Josée Brouillette**

DECLARATION OF CONSENT
Signature Page

I have read the contents of this consent form, and I agree to participate in this research study. I have had the opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given sufficient time to consider the above information and to seek advice if I choose to do so. I understand that I will be given a signed copy of this consent form. By signing this consent form, I am not giving up any of my legal rights.

The study doctor has my permission to tell my regular doctor about my being in this study and to relay any pertinent information arising from the study that may impact my care:
☐ YES ☐ NO

OPTIONS

Future Studies:
The long-term goal of this study is to design and conduct interventional studies that could potentially improve brain health in people living with HIV. We will then be recruiting participants from this cohort who meet the criteria of the interventional studies. Therefore participants in this study may be contacted at a future time and invited to participate in other studies. At that time you will be asked to sign a new informed consent form.

☐ I wish to be contacted to participate in other studies

☐ I **do not** want to be contacted to participate in any other studies

Neurocognitive Assessment:
A random sample of people will be selected to have a full neuropsychological assessment performed, in order to assess their cognition (concentration, memory, attention, problem solving). This will only be done once during the study and take 1.5 - 4 hours of your time. The testing entails the completion of several tasks to evaluate different cognitive functions (thinking, learning, and memory).
This is an optional aspect of the study and if you do not wish to participate please check the box below.

☐ I wish to participate in the full neuropsychological assessment if selected

☐ I **do not** wish to participate in a full neuropsychological assessment

_____	_____	_____
Participant's signature	Name (in block letters)	Date
_____	_____	_____
Signature of Person	Name (in block letters)	Date

Appendix 3: Informed Consent Form Cognitive Training Sub-study

INFORMATION AND CONSENT FORM FOR COGNITIVE TRAINING SUB-STUDY

Title:	**Understanding and Optimizing Brain Health in HIV Now**
Principal Investigators:	**Dr. Lesley Fellows & Dr. Marie-Josée Brouillette**
Study Site:	**Montreal Chest Institute (MUHC)**
Sponsor:	**McGill University** **Canadian Institute of Health Research (CIHR)**

INTRODUCTION

You have agreed to participate in the main study and are now being asked to participate in this cognitive training sub-study.

Before deciding to participate, you should understand the content of this consent form, the risks and benefits to make an informed decision, and ask questions if there is anything you do not understand. Please read this entire consent form that contains a full explanation of the study and take your time to make a decision. If you decide to participate in this study you will be asked to indicate your agreement. A copy of this form will be emailed to you.

BACKGROUND

HIV can have subtle but important effects on the brain, leading to difficulties in thinking and concentrating. Computer-based brain training has been shown to improve cognitive abilities (memory, concentration, attention) in some people with brain disorders. However, the effects of such training in people living with HIV are unknown.

PURPOSE OF THIS STUDY

The goal of this project is to determine the extent to which computer-based cognitive training can improve cognitive function in individuals living with HIV who are experiencing difficulties with memory, thinking or concentration. This study will also help us to establish whether people respond differently to the different parts of the training.

STUDY PROCEDURES

If you decide to participate in this sub-study, you will be asked to attend an extra session to review the information given to you at the start of the study of how to improve your brain health. At this

information session, you will also be assigned to start the training right away or at a later point in time, after you have worked on achieving a brain health goal.

If you are assigned to start cognitive training right away, you will undergo some additional cognitive testing and will be instructed on how to access the training program from a personal computer. If you are assigned to start the cognitive training later, you will be shown how to use the training program at this later point in time.

The computer-based training will last for eight weeks. It will involve 30-minute sessions, which must be carried-out five times per week. The computer training tasks can be performed anywhere you have access to internet on a computer. The training program is accessible online: you need to go to the study website and log in with the username that you will receive from the investigator (a screen name that contains no personally identifiable information). The training is built as a game where you earn points to advance to the next level and receive continuous feedback on your performance as you engage in cognitive exercises. A trainer will use the secure web portal to regularly check your progress and will provide online or telephone support if needed.

After the eight weeks of computer training, we will repeat the cognitive tests and ask you a series of questions about your experience with the training program. This should take about 1 hour.

If you were assigned to start the training program at a later point in time, you will still need to come in for the extra information session, undergo the additional cognitive testing (before and after completion of the program) and receive the proper instructions for its use.

Even after the end of the study, and regardless of the group to which you have been assigned, you will be able to keep training on the program as you wish.

POTENTIAL BENEFITS

The benefits of this intervention are unknown. It is however hoped that the information obtained from this study will lead to the development of better tools to access the effects of cognitive difficulties in people living with HIV. . There are no known physical or psychological risks associated with your participation in this study.

DISCONTINUATION OF THE STUDY BY THE INVESTIGATOR

The principal clinical investigators and/or the MUHC Research Ethics Board are entitled to terminate the study at any time without your consent. If this is the case, you will be given a full explanation.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is entirely voluntary, and if you refuse, your medical care and treatment will in no way be affected. If you choose to participate, you may change your mind and withdraw at any time. Again, this will not affect the medical care you receive in any way. Withdrawal from this sub-study will not affect your participation in the main study.

If you no longer wish to share your personal health information, you may cancel your permission at any time by contacting the study coordinator. If you cancel your permission during the study, no new

personal health information will be collected, and the data gathered to that point will continue to be used to evaluate the study results.

COMPENSATION

You will not be paid for taking part in this study. However, you will be compensated for the extra visits related to this sub-study. To help you cover your travel expenses, childcare and inconvenience, you will receive $20.00 for the extra information session and $40.00 for the extra cognitive testing session.

INDEMNIFICATION/COMPENSATION IN CASE OF INJURY

If you should suffer any injury following your participation in the research project, you will receive the appropriate care and services for your medical condition without any charge to you.

By accepting to participate in this project, you are not waiving any of your legal rights nor discharging the researchers (the granting agency, if applicable, depending on the type of research) or the institution of their civil and professional responsibility.

CONFIDENTIAL NATURE OF THE STUDY

The results of the testing will remain confidential in the strict respect of the law. They will be used exclusively for scientific research purposes and will be recorded and maintained in confidence by, and available only to, Dr. de Villers-Sidani and researchers working under his supervision.

All usage and progress data generated by the training will be encrypted and transmitted to a central server and backed up on a secured local server at McGill. The data will be available for review by Dr. de Villers-Sidani, Dr. Lesley Fellows and Dr. Marie-Josée Brouillette and researchers working under their supervision through a secure web portal. No personally identifiable information, including Internet protocol addresses, will be stored.

All personal information collected to enroll in the study will be kept separately from the encrypted data and the key-code will be kept securely under lock and in a separate location than the data. Following the collection of results, all data will be kept coded and securely on a local server at the Montreal Neurological Institute for seven (7) years and will only be available for review by Dr. de Villers-Sidani, Dr. Lesley Fellows and Dr. Marie-Josée Brouillette and researchers working under their supervision. No personal information will be released to third parties without your written approval.

You should also be aware that the Research Ethics Board or Quality Assurance Officers duly authorized by it may access study data.

Any secondary use of this data would be restricted to a research protocol in the same or related area of study and would be subject to approval of the Research Ethics Board.

Should any results be presented or published in scientific journals, you will not be identified by name.

By signing this consent form, you give us permission to release information regarding your participation in this study to these entities. Your confidentiality will be protected to the extent permitted by applicable laws and regulations.

Your confidentiality will be protected to the extent permitted by applicable laws and regulations in the Province of Quebec.

FUNDING OF THE RESEARCH PROJECT

The Canadian Institute of Health Research is providing infrastructure support for the conduct of this clinical research and is being run by Dr. de Villers-Sidani, Dr. Lesley Fellows and Dr. Marie-Josée Brouillette. The study doctors are not being paid for including you and looking after you during your participation in this study.

CONTACT INFORMATION

Should you wish at any time, now or later, to contact a person who can give you information about this research study, contact Dr. Étienne de Villers-Sidani at 514 398-8911 or Dr. Marie-Josée Brouillette at 514 843-2090.

If you have any questions regarding your rights as a research participant, and you wish to discuss them with someone not conducting the study, contact the McGill University Health Center Ombudsman at (514) 934-1934, ext 35655, who will provide you with independent advice.

Study title: **Understanding and Optimizing Brain Health in HIV Now**

Principal Investigators: **Dr. Lesley Fellows & Dr. Marie-Josée Brouillette**

DECLARATION OF CONSENT FOR COGNITIVE TRAINING SUB-STUDY

I agree to participate in the research study, which just has been described to me. I have read and understood the information presented above about the procedures, advantages and disadvantages involved in this study and have received satisfactory answers to my questions related to this study.
I have been given sufficient time to consider the above information and to seek advice. I will be given a copy of this signed and dated Informed Consent Form.

With full knowledge of all foregoing I agree, of my own free will, to participate in this study.

☐ I wish to participate in the cognitive training sub-study if selected
☐ I **do not** wish to participate in the cognitive training sub-study if selected

_____	_____	_____
Participant's signature	Name (in block letters)	Date
_____	_____	_____
Signature of Person Administering Informed Consent	Name (in block letters)	Date

Appendix 4. Educational material on brain health (*"Simple steps to brain health"*)

Positive Brain Health Now

Note to ethics: the web sites will be updated during the study to reflect the most up-to-date information available

www.brainhealthnow.mcgill.ca

8 SIMPLE TIPS FOR BETTER BRAIN HEALTH

Why is it important to focus on brain health?

The cognitive difficulties that can occur in people living with HIV are likely related to several factors. While some are not fully understood, we already know that others can be changed for the better. General measures to optimize brain health may go a long way to preserving and improving cognitive function.

Evidence shows that what is good for the body is also good for the brain. A healthy lifestyle, including engaging in stimulating activities, eating well, exercising regularly, managing stress and limiting problematic foods and drinks can help promote brain health.

Take a look at the **8 tips** in this document. These are tips that anyone can use, but only you know what is most important and relevant to your own life.

Begin by choosing just **one** area where you think you could start making a difference today. Check out the recommended website or call the number provided for more information on what to do and how to get started. Set yourself a realistic goal and give it a try for just a week or two. You may be surprised by how easy it is to build a healthier brain starting right now.

1. STOP SMOKING

Nicotine is a powerful drug that changes the brain as well as the body. While nicotine improves mood and energy within seconds, this soon subsides leaving smokers feeling tired and "down", in turn fueling the craving for another cigarette. Smoking also has negative effects on brain blood flow, reducing how much oxygen gets to the brain, and increasing the risk of brain damage from stroke.

It's never too late to stop smoking and enjoy the health benefits that will follow. After just two days of not smoking, brain function begins to improve, and stroke risk drops.

Visit the Canadian Cancer Society's website (www.smokershelpline.ca) for tools to help you quit smoking or call their smokers' helpline toll free at 1-877 513-5333.

Visit http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/quit-cesser/index-eng.php or http://www.catie.ca/en/catienews/2011-11-08/understanding-tobacco-addiction for more information on the effects of smoking.

If you will only make one of the changes suggested here, this should the one!

2. CHALLENGE YOUR MIND

Do mentally challenging activities each day. Play cards or board games with friends. Do puzzles and crosswords to keep your thinking sharp. Nurture creative thinking through hobbies and crafts. Learn a new language or take up line dancing!

Visit http://www.catie.ca/en/fact-sheets/other-health-conditions/hiv-and-brain or http://www.alzheimer.ca/en/About-dementia/About-the-brain/Brain-health for more ways to stimulate your mind.

3. LIMIT ALCOHOL & STREET DRUGS

In the short term, alcohol can result in trouble walking, slowed reaction times, poor sleep, and memory problems. Over time, drinking large amounts of alcohol results in permanent brain damage and limits the growth of new brain cells. Women may be especially at risk.

Some studies have suggested small amounts of alcohol might benefit brain function (e.g., 125 ml wine daily), but regular alcohol consumption also raises the risk of problems like high blood pressure, some cancers, and stroke. IF you chose to drink, limit consumption to no more than 2 drinks for men and 1 drink for women per day.

Cannabis, opiates, and stimulants can all lead to cognitive difficulties.

Learn more about the effects of alcohol and street drugs consumption at http://www.catie.ca/en/practical-guides/managing-your-health/4 or http://www.cpha.ca/en/portals/substance/health.aspx

4. MOVE YOUR BODY

Brain health is directly tied to physical health and can improve with exercise. Be active. You can improve your health with as little as 2.5 hours of moderate to vigorous aerobic activity each week, broken into sessions of 10 minutes or more. Get stronger by adding strengthening activities such as push-ups, leg squats and abdominal crunches that target your muscles and bones at least two days per week.

The best effects on brain health are seen when aerobic and strength training are combined.

Visit http://www.catie.ca/en/practical-guides/managing-your-health/4#exercise, http://www.catie.ca/en/treatmentupdate/treatmentupdate-186/hiv-brain/exercise-found-improve-memory or www.phac-aspc.gc.ca/hp-ps/hl-mvs/pa-ap/07paap-eng.php for ways to get active.

5. GET A GOOD NIGHT'S SLEEP

Your brain is very active during sleep. A good night's sleep helps improve memory and the ability to learn new information. To sleep well, it's important to follow a regular sleep schedule. Develop a consistent routine and go to bed at the same time every day. Avoid naps during the day that can make it harder to fall asleep at night.

Limit stimulants like coffee, cola and even chocolate, and try avoiding them entirely after 4 pm. Avoid eating large meals or exercising close to bedtime.

Talk with your doctor if you have trouble falling asleep, wake too early in the morning, sleep too much for two weeks or more or if your sleep is chronically poor. Loud snoring may also be a sign of more serious sleep disorders that may need medical treatment.

Learn more about health sleep habits at: http://www.catie.ca/en/positiveside/winter-2013/sleep-tight

6. MANAGE STRESS AND NEGATIVE MOODS

You can't eliminate stress, but you can learn to identify sources of stress and respond to stressful situations in healthier ways. Learn to reduce your stress by setting realistic goals and managing your time effectively.

Deep breathing and other relaxation techniques, mindfulness meditation, and physical activity can help quiet the body and the mind. Yoga and other mind-body activities may be especially good ways to promote mental and physical relaxation.

Anxiety and depression will definitely affect your memory and your ability to think clearly. Speak with your healthcare provider if you feel anxious or sad most of the time for two or more weeks. Effective treatments include regular physical activity, short-term talk therapy or medication.

Learn more about managing stress and negative moods at http://www.catie.ca/en/practical-guides/emotional-wellness orhttp://www.cmha.ca/mental-health/

7. EAT A HEALTHY DIET RICH IN FRUITS AND VEGETABLES

Nutritious foods that are healthy for your heart are also good for your brain. Protect brain health with foods high in antioxidants like spinach, kale, broccoli, red peppers, berries, coldwater fish like salmon, and almonds.

Limit foods high in fat and cholesterol. Bake or grill instead of frying. Use olive oil instead of butter.

Drink plenty of fluids to avoid dehydration. Water is the ideal way to add fluids without increasing calories.

Learn more about healthy eating at http://www.catie.ca/en/practical-guides/managing-your-health/4#eating, http://www.catie.ca/en/practical-guides/nutrition or http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php

8. REVIEW YOUR MEDICINES WITH YOUR DOCTOR

Many medicines, including drugs prescribed for heart conditions, antihistamines, certain diabetic medications, muscle relaxants, antacids, and antidepressants, along with some over-the-counter drugs, can negatively affect memory and thinking.

Ask your health care provider to review the medicines you are taking to minimize cognitive side effects. Speak up right away if you notice new medications are leading to more problems with memory or thinking.