

Full Title: Efficacy potential of goal management training to improve cognitive function in older people living with HIV

Abbreviated title: Goal Management training in people living with HIV

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## PROTOCOL SUMMARY

Full Title	Efficacy potential of goal management training to improve cognitive function in older people living with HIV
Short title	Goal Management training in people living with HIV
Sponsor	McGill University Health Centre
Funding	Canadian Foundation for AIDS Research (CANFAR)
Principal Investigators	Dr. Marie-Josée Brouillette & Dr. Lesley Fellows
Associate investigators	Dr. Brian Levine & Dr. Nancy Mayo
Primary Objectives	<ol style="list-style-type: none"> <li>1. Determine the feasibility and acceptability of GMT in people with stable HIV infection who report cognitive concerns</li> <li>2. Provide preliminary evidence of the effect of GMT on cognitive performance, compared to a waitlist control group, as measured by (i) cognitive performance tests and (ii) self-report questionnaires</li> </ol>
Study Population	<p><b>Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Age <math>\geq 45</math></li> <li>• HIV infection for at least 1 year</li> <li>• Able to communicate in English or French</li> <li>• Capable of providing informed consent</li> <li>• Subjective complaints of cognitive difficulties</li> <li>• Evidence of cognitive deficit (B-CAM score <math>\leq 24</math>)</li> </ul> <p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Dementia (MSK-rating stage 3 or more-cognitive component only)</li> <li>• Concern about capacity to consent</li> <li>• Life expectancy of <math>&lt; 3</math> years or other personal factor limiting the ability to participate in follow-up</li> <li>• Non-HIV-related neurological disorder likely to affect cognition</li> <li>• Known active CNS opportunistic infection or hepatitis C requiring IFN treatment during the follow-up period</li> <li>• Known psychotic disorder</li> <li>• Current substance dependence or abuse within the past 12 months.</li> </ul>
Study Design	Observational
Sample Size	60
Study Duration	1 year

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## EFFICACY POTENTIAL OF GOAL MANAGEMENT TRAINING TO IMPROVE COGNITIVE FUNCTION IN OLDER PEOPLE LIVING WITH HIV

### Background information

People living with HIV worry about their memory, and with good reason. It is now clear that this chronic illness can have disabling effects on cognition, even with excellent systemic viral control (1). Although the burden of cognitive impairment 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% (1, 2). 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 (3). Impaired cognition can affect medication adherence (in turn posing a public health risk for the spread of HIV), occupational and social function, quality of life, and even accelerate mortality (4, 5). We are only beginning to understand this emerging co-morbidity, which is likely the result of multiple interacting processes, including chronic neuroinflammation, premature cerebrovascular disease, neurotoxic effects of drug treatment, and co-existing mental health issues (1).

Given these hypotheses, the field has assumed that cognitive impairment in HIV is likely to be progressive, in fact our own work using the CHARTER data shows this is not generally the case. Although 246/701 in the longitudinal cohort were classified as cognitively impaired at baseline, only 16% (N=111) showed decline at 3 years, most of the time on a single neuropsychological test. This observation suggests that for the majority of people, mild cognitive impairment may be a relatively static condition. On-going work in several countries aims to better understand the factors contributing to cognitive impairment in older people with HIV, including a CIHR-funded project we are currently leading [Positive Brain Health Now (+BHN), <http://brainhealthnow.mcgill.ca>]. However, we need not wait for a full understanding of the determinants of cognitive impairment to take action; patients with these difficulties need solutions **now**. Testing the impact of available interventions can establish what works, and can also help us understand whether the impact of brain injury in HIV can be mitigated to preserve function and quality of life.

Rehabilitation is a well-established approach to maintain function in the face of chronic disease, and holds promise for addressing the health challenges faced by older people with HIV (6). A Canadian-led knowledge synthesis review published in 2014 identified cognitive rehabilitation as a promising approach in HIV, but highlighted the absence of high quality, HIV-specific evidence in this area (7). A recent focused review also highlights the dearth of evidence on this topic (8). Very few studies have been published, and to date all have been restricted to computerized training programs only (8). While there is limited evidence for computerized cognitive rehabilitation in any context, there is better evidence for more conventional, in-person rehabilitation approaches, at least in other neurological disorders. Although computerized training is appealing because it is more feasible to deliver on a wide scale than conventional cognitive rehabilitation, we propose that the first step should be to establish an evidence base regarding the efficacy of any form of cognitive rehabilitation in HIV. Evidence of efficacy of a 'high dose' established rehabilitation method could be followed by work to define the key elements, and to study how those elements could be delivered most cost-effectively, but there is no point in pursuing these secondary steps if the most well-established cognitive rehabilitation approaches do not show efficacy. Thus, we propose to test conventional rehabilitation as a crucial first step is a research program focused on evidence-based interventions for improving brain health in HIV.

There is no gold standard conventional cognitive rehabilitation program, but most existing approaches combine face-to-face therapy with at home practice over a period of at least several weeks. In the absence of a gold standard, we have selected one such program: Goal Management Training (GMT). This

program targets executive dysfunction, which is a central problem in HIV-associated neurocognitive disorder (8, 9). GMT is grounded in a neurobiological framework and was developed based on nearly two decades of research on practical approaches to minimizing the impact of executive dysfunction, aiming to help people with brain injury manage real life tasks. The program teaches self-management principles, stress management and mindfulness, and trains participants in the use of several explicit strategies to reduce cognitive load in everyday tasks, and methods to cue attention to maintain focus on specific tasks. GMT is now a manualized protocol with set content conveyed through a combination of slides and a workbook. Two-hour small group sessions are led, in person, by a trained therapist either once twice a week, for seven weeks. The small group sessions allow participants to learn from each other, enhancing engagement. GMT has been shown to improve cognitive function in a variety of neurological conditions, as well as in healthy older people with cognitive concerns (10-13). Evidence from randomized trials shows that this intervention leads to (i) significant improvements in performance on cognitive tests, including naturalistic tests of real life tasks, (ii) reduced self-reported cognitive concerns (10, 11, 14), and (iii) significant improvements in everyday function (11-13, 15) compared to either a wait-list condition or a general brain health education control. Positive effects have been found in older people with cognitive concerns, and neurological populations with mild cognitive impairment including mild traumatic brain injury (10), stroke (11) and spina bifida (14, 15). These improvements have been shown to last at least 6 months in some studies (13-15) and are accompanied by changes in the brain networks underlying executive function (16). GMT is thus a well-validated, high yield intervention with which to test the potential of cognitive rehabilitation in older HIV+ people with cognitive concerns.

### Clinical Significance

The proposed project brings together a high profile multidisciplinary team to perform the first randomized controlled study of in-person cognitive training in the HIV population. The core platform is a low burden observational study that aims to understand and address the heterogeneous, multi-factorial nature of compromised brain health in people living with HIV. The pilot project is cost- and time-effective, nested within this ongoing observational cohort study. A standardized intervention will be used, supported by good evidence of efficacy in studies involving other neurological disorders with similar profiles of cognitive impairment. Dr. Levine (co-I) had a pivotal role in the validation of the GMT intervention and is an expert in the area of cognitive training. Our team also has extensive experience with all of the project requirements, including HIV clinical trials, large-scale health outcomes research, data management, and advanced statistical methodologies. Addressing or preventing cognitive impairment is a pressing concern for people living with HIV, and those who care for them. Cognitive training is resource consuming and not the standard of care in HIV. High quality evidence is needed to justify committing resources to such training. We propose work that directly addresses this need, taking advantage of the ‘window of opportunity’ provided by the on-going +BHN project. Regardless of the outcome, this study will provide important information to orient future work aiming to improve cognition in people living with HIV. The results of this pilot study will inform the development of a full randomized controlled trial.

### Study Hypothesis

We hypothesize that GMT, a cognitive rehabilitation intervention, will lead to improved cognitive function as assessed by better performance on cognitive tests and reduced cognitive concerns in people with stable HIV infection who report cognitive concerns at baseline, compared to a wait-list group.

## Study Objectives

The specific objectives of this study are to:

1. Determine the feasibility and acceptability of GMT in people with stable HIV infection who report cognitive concerns
2. Provide preliminary evidence of the effect of GMT on cognitive ability, as measured by changes in (i) cognitive performance tests and (ii) self-report questionnaires.

## STUDY DESIGN

This is a concurrently controlled trial. Study participants will be randomly selected from those participating in the ongoing, longitudinal +BHN study at 2 sites in Montreal (The Montreal Chest Institute and L'Actuel Medical Clinic). This CIHR Team Grant-supported observational, prospective cohort study is enrolling consecutive patients attending 5 HIV clinics across Canada for a total sample of 900, followed every 9 months for 27 months. Inclusion criteria are: age 35 y or older, HIV infection for at least 1 year, able to communicate in English or French and capable of providing informed consent. Exclusions are presence of dementia, life expectancy < 3 y, other neurological disorder including active opportunistic CNS infection, psychotic disorder, current substance dependence or abuse, and Hepatitis C requiring interferon therapy during the study period. Montreal sites will enroll 350 participants, which should provide an adequate pool for recruitment to this sub-study.

The GMT intervention will be tested in a randomly selected sub-group (N=30) of this cohort who meet the following additional criteria: over age 45, subjective complaints of cognitive difficulties, and performance on objective computerized cognitive tests that falls at or below the 50th percentile of performance in the cohort as a whole (as measured by the cohort study's primary outcome, a combination of self-report and performance items called the Brief Cognitive Ability Measure [B-CAM] (17)). The concurrent control group will be comprised of those eligible for GMT but not randomly selected.

## Procedure

Participants will be recruited at the time of their routine +BHN study visit, at which comprehensive information about their current health status, function, quality of life, cognitive concerns, and cognitive performance is already being gathered. Following informed consent, all participants will complete a short set of neuropsychological tests and questionnaires that have been shown to be sensitive to the effects of GMT [Sustained Attention to Response Task-SART (18), Tower of London (19), and Dysexecutive Questionnaire-DEX (20)] immediately, or at a visit arranged for this purpose, separate from the +BHN main study. Participants will then begin GMT, as described below. Within 4 weeks of completing the GMT program, they will be asked to repeat the neuropsychological testing and complete additional tests which form part of the standard +BHN visit at a second study visit, coincident with the +BHN study visit if timing permits.

## Intervention

The standard GMT program lasts 9 weeks and involves 9 weekly 2-hour small group sessions led by a trained therapist. It follows a manualized program that teaches participants a series of techniques to build attention and executive function, and shows them how to implement these techniques in their everyday life. The small group sessions allow individualization of the training to show how it can be applied to

meet the particular challenges reported by participants, and explicitly encourage participants to share their challenges and successes with others in the group to promote learning and engagement with the program. The sessions are reinforced with homework, in which participants practice what they have learned. Sessions will be audiotaped for later review by the trainer and/or study investigators to ensure adherence to the intervention manual. The material, including homework, is provided in a workbook that participants use throughout the training, and keep for later reference.

## **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**

The feasibility and acceptability of the GMT will be evaluated in the whole group (N=30) based on the proportion of GMT sessions attended, the proportion of the homework completed, and the overall level of satisfaction with the program, as determined by an anonymous questionnaire filled out by the participants at the end of the intervention.

The potential impact on cognition of GMT will be evaluated in two ways: (i) a within-person analysis of change in cognitive outcomes after all persons have completed the GMT program; and, for exploratory purposes, (ii) a between group comparison contrasting change in cognitive outcomes between the GMT group and the concurrent control group assessed in the main study.

For all analyses, the B-CAM (performance measure) will be the primary cognitive outcome and a global outcome response will be based on changes in the B-CAM and on four secondary cognitive outcome measures: SART, Tower of London, Dysexecutive Questionnaire-DEX and PDQ.

For the within-person analysis, change from pre-to post will be calculated for each person and a 95% confidence interval (CI) around the mean change will be calculated. A 95% CI that excludes 0 indicates statistically significant change. A sample size of 30 will provide 80% power to detect an average standardized response mean (effect size for change) of 0.38, within the reported range for GMT in other conditions. However, average change is not very interpretable as this average change can occur in many ways including no change for a lot of people and large change for a few, or even deterioration for some. To provide a more interpretable estimate of treatment impact, an overall effect will also be reported, based

on the proportion of individuals who improved at least 0.5 SD on one of the cognitive outcome measures. A change of 0.5 SD is considered clinically relevant (21). For this analysis, generalized estimating equations (GEE) will be utilized to adjust for a possible correlation between the different measures. The outcome will be the binary response for each of the five cognitive outcomes, and the analysis yields an estimated charge proportion adjusted for non-independence. Having five outcome measures increases the number of observations available for analysis by a factor of 1.8, termed the design effect. The design effect (22) is a function of the number of measures (here  $m-1$ ) and the correlation between measures (estimated at 0.2). Hence the number of observations effectively available for analysis is  $30 \times 1.8$  or 54. With this sample size, the 95% CI will exclude a low responder proportion (20%) as long as the responder proportion is greater than 28% ([www.vassarstats.net](http://www.vassarstats.net)).

For the between-group analysis, 30 people in the intervention group and a concurrent control group of 100 (with five outcome measures, the effective sample size is inflated by the design effect of 1.8). Thus, using all measures, the sample would provide 80% power to detect an effect size of 0.4 (0.4 of a SD). For this analysis, generalized estimating equations (GEE) for a continuous outcome will be utilized to adjust for a possible correlation between the different measures. Each measure will be transformed onto a 0 to 100 scale for permit a global intervention effect to be estimated.



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