

**Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

Full Title:	Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study
Abbreviated title:	HIV and CPAP
Funding:	The current study is sub-study of the Canadian Institute of Health Research (CIHR)-funded study “Understanding and Optimizing Brain Health in HIV Now”.  CPAP devices and masks for the duration of the study are provided in-kind by Resmed and cost of visits related to its initiation and calibration are provided in-kind by VitalAire
Principal Investigators:	Dr. Marie-Josée Brouillette & Dr. Lesley Fellows Glen Site-D02.4110 Chronic Viral Illness Service McGill University Health Centre Montreal, Quebec H4A 3J1
Associate investigators:	Dr Cecilia Costiniuk Glen Site-D02.4110 Chronic Viral Illness Service/Division of Infectious Diseases McGill University Health Centre  Dr Marta Kaminska Respiratory Division/Sleep laboratory 1001 Decarie Blvd Montreal, Quebec H4A 3J1
Study design and statistical analyses:	Dr. Nancy Mayo Royal Victoria Hospital, Room 4.29 687 Pine Avenue West Montreal, Quebec H3A 1A1

**Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

**PROTOCOL SUMMARY**

Full Title	Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study
Short title	HIV and CPAP
Sponsor	McGill University
Funding	Canadian Institute of Health Research (CIHR) CPAP and masks for the duration of the study are provided in-kind by Resmed and cost of visits related to its initiation and calibration are provided in-kind by VitalAire
Principal Investigators	Dr. Marie-Josée Brouillette, Dr. Lesley Fellows, Dr. Nancy Mayo
Associate investigators	Dr. Cecilia Costiniuk, Dr. Marta Kaminska
Objectives	<p>The primary objective is to estimate among people with HIV and obstructive sleep apnea, the extent to which 4-7 months of CPAP impacts on the primary outcome of cognitive ability (B-CAM), in comparison to individuals who screen positive for OSA but are not participating in the sleep apnea intervention.</p> <p>An exploratory objective is to identify whether the changes are similar on measured cognitive ability and on self-reported cognitive symptoms.</p> <p>The explanatory objective is to relate degree of adherence to CPAP to change in cognitive outcomes.</p>
Study Population	<p><b>Inclusion Criteria</b></p> <ul style="list-style-type: none"><li>• Participants in the cohort study “Understanding and Optimizing Brain Health in HIV Now”</li><li>• Screened positive for OSA using the Berlin or the STOP-BANG (completed as part of the main study visits)</li><li>• Have been on a stable HAART regimen for &gt; 6 months</li><li>• B-CAM ≤ 29</li><li>• Have not had a change in medications that could potentially interfere with sleep or cognition in the past 4 months.</li><li>• Willing to use CPAP as per instructions</li><li>• Able to comply with follow-up visit assessments</li><li>• Able to communicate in English or French</li><li>• Have at least one remaining visit in the main cohort study</li></ul> <p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"><li>• Already treated for OSA</li></ul>

**Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

	<ul style="list-style-type: none"><li>• Ongoing involvement in night shift work</li><li>• Presence of restless legs syndrome requiring immediate specific treatment</li></ul>
Study Design	Quasi-experimental single-arm, pre-post design will be carried out over a period of 4-7 months.
Sample Size	30 participants have used the CPAP device for a minimum of 4 months, on at least 30% of the nights with a median use of $\geq 4$ hours/night.
Participant involvement	Up to 12 months

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

### **BACKGROUND**

Cognition and HIV: 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 cognition, even with excellent systemic viral control. The cognitive disturbances observed in HIV infection fall under the broader term HIV-associated neurocognitive disorders (HAND). Although the prevalence of HAND in Canada is unknown, it is likely to be high. Recent studies in other developed countries report a prevalence of cognitive impairment of 30-50% [1, 2]. Even higher rates have been documented in those over the age of 50, a rapidly expanding group.

There is currently no treatment for HAND. However, it is now recognized that HIV infection is associated with several medical conditions that independently contribute to cognitive disturbances. Identification and treatment of potentially reversible contributors to cognitive impairment is therefore key to the clinical management of these cognitive difficulties.

Definition of obstructive sleep apnea: Obstructive sleep apnea (OSA) is a breathing disorder that is characterized by episodes of complete or partial cessation of respiration during sleep, associated with upper airway collapse, oxygen desaturation and sleep fragmentation [3]. The index commonly used to assess sleep disordered breathing (SDB) is the respiratory disturbance index (RDI), defined as the average number of respiratory disturbances (obstructive apneas, hypopneas, and respiratory event-related arousals [RERAs]) per hour. According to the Centers for Medicare & Medicaid Services criteria for the positive diagnosis and treatment of obstructive sleep apnea, a positive test for OSA is established if the RDI  $\geq 15$  events per hour [4].

Obstructive sleep apnea and cognition: Obstructive sleep apnea (OSA) is a condition frequently implicated in cognitive disturbances [3, 5-10]. These cognitive deficits are common : for example, in a meta-analysis of individuals with OSA, information processing speed was reduced in as many as 75% of individuals compared with norm-referenced data [6]. In addition to its negative impact on cognition, OSA is associated with health conditions such as hypertension, metabolic disturbances (including impaired glucose tolerance, insulin resistance and dyslipidemia) and heightening risk of heart disease, stroke and mortality [11-13], conditions also increased in persons living with HIV. Individuals suffering from OSA report an increase in daytime sleepiness, mood changes and decline in quality of life [6-10]. OSA also portends economic and societal impact through lost productivity at work and motor vehicle accidents [14]. The presence of OSA is therefore important to detect in those living with HIV as it is a potentially treatable contributors to cognitive disturbances in HIV.

Obstructive sleep apnea and HIV: General population estimates of moderate to severe sleep-disordered breathing depend on criteria used and vary widely [15], from 6-13% of individuals [6, 16], to up to 23% of women and 50% of men [17] using modern criteria. This prevalence is increased in the HIV population. Based on data from the Multicenter AIDS Cohort Study (MACS, N=1896) and Women's Interagency HIV Study (WIHS, N=1976), HIV-infected individuals are more likely to be diagnosed with OSA than HIV-uninfected individuals when confounders such as age and body mass index were accounted for (Prevalence Ratio (PR) 1.42; p=0.01 and PR 2.10; p=0.002, respectively)

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

[18]. HIV-infected individuals have many risk factors for OSA including a high rate of obesity: >60% of HIV-infected women in the WIHS and >40% of HIV-infected men and MACS [19].

Traditional risk factors associated with OSA include advanced age, male gender, large neck circumference, obesity and hypertension [13]. However, these traditional clinical indicators of OSA may be less salient in the presence of HIV infection. In a large observational study, those with HIV and OSA were more likely to be younger, have lower body-mass-indexes and were less likely to have hypertension than those without HIV infection [20]. As a result of this different risk profile, the presence of OSA in HIV+ individuals was more often undiagnosed [20], underscoring the need for a higher index of suspicion in the presence of HIV infection.

Treatment of obstructive sleep apnea and its impact on cognition: Continuous Positive Airway Pressure (CPAP) is the recommended treatment of choice for OSA. A CPAP device includes a pump which delivers air via a mask covering the nose or mouth while a person is sleeping [21]. The flow of air generates positive pressure, which opens the airways, preventing soft tissue collapse [21].

CPAP has established efficacy in improving cognition. A meta-review involving review articles meeting pre-determined strict criteria, concluded that CPAP use improved executive function, long-term verbal and visual memory, attention/vigilance and global cognitive functioning [22]. Another meta-analysis also found that individuals with OSA demonstrated medium to very large impairments executive dysfunction, independent of age and disease severity, which showed small to moderate improvements following CPAP treatment [23]. In the context of Alzheimer's disease, Ancoli-Israel et al. conducted a randomized double-blind placebo-controlled trial to determine whether CPAP use resulted in improvements in neuropsychological test scores. Although the study was underpowered to make definitive conclusions about improvements within specific cognitive constructs, exploratory post hoc examination of score changes suggested that CPAP use by individuals with OSA yielded some benefits; these included improvements in episodic verbal learning and memory and some aspects of executive functioning such as cognitive flexibility and mental processing speed [24].

Although CPAP has been associated with improvements in cognitive functioning in the general population, its effectiveness in improving cognition in HIV+ individuals has never been previously tested. Given that the cognitive disturbances in this population are multi-factorial, determining whether treatment of OSA in this population improves cognition is key in improving the clinical management of HIV+ individuals, both for its negative impact on cognition but also more generally for their health.

Obstructive sleep apnea in the cohort “Understanding and Optimizing Brain Health Now”. Cohort participants (N=840) are studied prospectively over a 27-month period with visits every 9 months. Patients complete a computer-based evaluation of cognitive ability, the B-CAM, as well as questionnaires on socio-demographic characteristics, symptom status, functional status, health perception and quality of life. Given the high prevalence of OSA reported in the population, participants complete questions that, combined with other values already documented, support the scoring of two screening questionnaires for OSA, the Berlin [25, 26] and the STOP-BANG [27, 28] (see

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

Appendix 1). Selected cohort members at the Montreal sites who screen positive for the presence of OSA will be invited to participate in the study.

### **STUDY OBJECTIVES**

The overall aim is to contribute evidence about the impact of treatment of sleep apnea (with CPAP) on cognitive ability in HIV+ individuals.

The primary objective is to estimate among people with HIV and obstructive sleep apnea, the extent to which 4-7 months of CPAP impacts on cognitive ability (B-CAM), in comparison to individuals who screen positive for OSA but are not participating in the sleep apnea intervention.

An exploratory objective is to identify whether the changes are similar on measured cognitive ability and on self-reported cognitive symptoms.

The explanatory objective is to relate degree of adherence to CPAP to change in cognitive outcomes.

### **STUDY HYPOTHESIS**

Given there is no expectation for improvement in cognitive ability in this population in the absence of treatment for sleep apnea, we hypothesize that, over 4-7 months weeks of CPAP use, an improvement in cognition will occur, and if this is observed in 7 or more of 30 people, this response frequency is unlikely to have occurred by chance.

### **STUDY DESIGN**

This study is part of a larger project based upon a cohort multiple randomized controlled design [29]. Within a fully characterized cohort (N=840) which is followed over time, people meeting the specific criteria for one or more interventions (here CPAP) are identified and a sample is randomly selected to receive the intervention; the remaining eligible persons who do not receive the intervention serve as controls. This design, when operationalized for one intervention, yields three cohorts: (i) the intervention cohort comprising all those approached who agreed to enter; (ii) the refuser cohort comprising all those approached who declined entry; and (iii) control cohort comprising eligible persons who were not approached, and hence were not given the opportunity to accept or decline. For the CPAP intervention, the duration of the study is 4-7 months.

Eligible patients will be identified among the Montreal participants (N=500) in the “Understanding and Optimizing Brain Health Now” cohort study who have screened positive for the possible presence of sleep apnea on either the Berlin or the STOP-BANG and experience some cognitive difficulties as measured by the B-CAM ( $\leq 29$ ). We will continue recruitment until 30 participants have used the CPAP device for a minimum of 4 months, on at least 30% of the nights with a median of  $\geq 4$  hours/night.

### **Eligibility criteria**

#### **Inclusion criteria**

- Participants in the cohort study “Understanding and Optimizing Brain Health in HIV Now”

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

- Screen positive for the presence of OSA with either the Berlin or the STOP-BANG
- Have been on a stable HAART regimen for > 6 months
- B-CAM score ≤ 29
- Have not had a change in medications that could potentially interfere with sleep or cognition in the past 4 months.
- Willing to use CPAP as per instructions
- Able to comply with follow-up visit assessments
- Able to communicate in English or French
- Have at least one remaining visit in the main cohort study

### **Exclusion criteria**

- Already treated for OSA
- Ongoing involvement in night shift work
- Presence of restless legs syndrome requiring immediate specific treatment

### **Screening:**

Brain Health Now study participants who screen positive for the presence of OSA, meet inclusion/exclusion criteria based on the information already available as part of the main study questionnaires and who, on initial enrolment, have agreed to be contacted for sub-studies, will be approached for participation. Those who agree to participate and provide informed consent will be referred for a polysomnography (sleep study). Those with confirmed OSA will continue to the intervention phase.

### **Intervention (CPAP)**

Participants will be evaluated by a sleep specialist who will confirm eligibility for CPAP treatment. Eligible participants will be referred to VitalAire for initiation of treatment, following a standard protocol for use in the home (see Appendix 2). CPAP treatment will continue until the next visit for the main study, between 4-7 months based on the timing of the evaluations, after which the OSA study will end.

### **Post Intervention**

At the end of the study, participants will be referred to the sleep clinic where the sleep nurse will facilitate obtaining a device as per usual clinical care (private insurance, self-funded, welfare, second hand, etc). Participants who opt to buy the CPAP machine that they have been using will have a 20% discount. There may be a gap between the end of the study and allocation of a new device; this fact is mentioned in the informed consent document. All participants will be able to keep their mask.

### **Measurement**

Four types of measures are under study: (i) cognitive ability; (ii) self-reported cognitive symptoms; (iii) adherence to the CPAP treatment; and (iv) cohort.

- (i) Cognitive ability will be measured using the B-CAM which comprises computerized cognitive tests and yields a score on a continuous metric [30].

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

The values to be used will be those collected during the scheduled platform evaluations which occur 9-12 months apart.

- (ii) Self-reported cognitive symptoms will be measured using the C3Q (Communicating Cognitive Concerns in HIV) collected during the scheduled platform evaluations which occur 9-12 months apart.
- (iii) Adherence to the CPAP home treatment will be obtained from the CPAP device directly through its telemonitoring function, which is done by activating modems on CPAP machines and having the data transferred onto the Compliance Management Solutions. The granularity of the data will yield a continuous metric of sleep-minutes of use. Reasons for poor adherence and tolerance will be obtained by telephone contact or at clinical visits with the sleep specialist.
- (iv) Three cohorts will be compared: (i) the intervention cohort comprising all those approached who agreed to enter; (ii) the refuser cohort comprising all those approached who declined entry; and (iii) control cohort comprising eligible persons who were not approached, and hence were not given the opportunity to accept or decline.

### **Procedures**

Patients diagnosed with OSA will be referred to VitalAire, a company that has agreed to loan Resmed CPAP devices, free-of-charge, to participants in this study (Appendix 3: Confirmation of collaboration). Staffs at VitalAire are under legal obligation to protect the confidentiality of information. Procedures for use of the devices will be explained to the patients. Follow-up with VitalAire staff will be done according to standard clinical protocols (see attached, Appendix 2). Patients may have as many visits with the respiratory therapist of VitalAire as needed for adjustments to their devices, at no cost. Typically patients will be contact by telephone one week after initiation and have follow-up in person with VitalAire after 1 month of CPAP use, but this may vary according to needs and availability.

During the course of CPAP use, the device automatically monitors various parameters which are used to monitor compliance in addition to residual apnea/hypopnea index (AHI) to ensure the settings are optimal. These data are obtained on line via the telemonitoring function and communicated by VitalAire to the study team. A separate consent will be signed at the same time as the consent for the OSA study, giving staff at VitalAire permission to communicate information to the study team (see Appendix 4).

As part of routine clinical care, patients will have a follow-up with a sleep specialist three months into the initiation of their CPAP to verify their clinical status and troubleshoot any issues with CPAP use. Additional visits will be scheduled if needed. A visit will also occur at the end of the study to plan post-study treatment.

### **Statistical Analysis and Sample**

Basic descriptive statistics will be used to characterize the participants including values on the all outcomes. Each person will be classified as a cognitive responder or not based on change on B-CAM. Responder status will be defined as improvement of  $\frac{1}{2}$  SD in B-

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

CAM score and C3Q. The analysis will focus on estimating the proportion of responders. A sample size of 30 participants will provide sufficient power for within-group analysis. 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, with 80% power and  $p<0.05$ , if 7 or more persons respond (stattrek.com binomial calculator.) The proportion of responders on the different cognitive outcomes will also be estimated.

A secondary analysis will relate adherence to CPAP to change in cognitive outcomes using linear regression adjusting for age, sex, weight, baseline sleep satisfaction.

For between-cohort comparisons of cognitive outcomes, generalized estimating equations (GEE) will be used to permit both the baseline and post-intervention measures to be included along with the within-person correlation. A linear GEE will be used as the outcomes are continuous although a binary response was used for the primary objective. The model will include the indicator variable for cohort (CPAP, refuser, or control), time (assessment 1, 2), as well as confounding variables of age, sex, education, BMI, and comorbidity. As the control cohort will be very much larger than the intervention cohort, statistical comparisons have sufficient power to detect effect sizes of 0.5 or greater, suitable for a pilot study. The parameter estimated from GEE is equivalent to an adjusted effect size (adjusted between cohort effect divided by correlation adjusted standard error).

### **Potential Risks and Benefits**

CPAP is the standard of care treatment for sleep apnea; what is under study here is its impact on cognition in HIV+ individuals. Possible side effects of CPAP or problems related to sleeping with a mask may include a transient sensation of difficulty breathing, bloating and gas in the morning, headaches or sores on the nose due to improperly adjusted mask, skin allergy to the mask, runny nose, dry or irritated eyes and dry mouth. These are usually minor and reversible. Assessment and troubleshooting is also routinely done automatically by staff at VitalAire and by the sleep specialist at the follow-up visits. CPAP therapy may need to be discontinued if side effects are intolerable despite best efforts to correct them (this occurs very rarely).

No reimbursement is provided for visits. Benefits include prompt access to polysomnography (for which there is a wait that can be as long as one year when done in hospital), free access to a CPAP device and close monitoring for the duration of the study for 4-7 months. After the end of the study, patients will have usual clinical follow-up in the MUHC sleep clinic, including discussion with the sleep nurse regarding available resources for obtaining a CPAP device-but we cannot ensure that there will not be a gap between the end of the study and the availability of a suitable CPAP device. A discount of 20% will be provided at VitalAire for participants who opt to buy their device. All participants will be able to keep their study mask.

### **Anticipated results, clinical significance and next steps**

We anticipate that this pilot study will demonstrate that a research study involving CPAP use is warranted and feasible in HIV-infected patients with OSA as judged by proportion of response and adherence. We also expect to find improvements in cognitive ability and cognitive symptoms following CPAP implementation. The findings from this pilot study

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

will inform a larger, more comprehensive study into the use of CPAP as a tool to improve neurocognitive outcomes in HIV+ individuals. Understanding whether cognition in persons living with HIV and OSA can be improved through the use of CPAP is important since this is a potentially modifiable risk factor with implications at both the individual and societal levels.

### **ETHICS/ PROTECTION OF HUMAN SUBJECTS**

#### **Informed consent**

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. 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 original signed informed consent form will be retained in the subject's study files and a copy will be provided to the subject. Participants will also be asked to sign a consent giving permission to VitalAire permission to communicate information to the study staff; that consent will be sent to VitalAire.

#### **Participant Confidentiality**

As the CPAP treatment is clinically indicated, nominal information will be communicated to VitalAire in order to allow ongoing communication with the participant and the respirologist overseeing treatment. All research records will be kept in a secure, locked location and only research staff will have access to the records. Upon request, clinical information may be reviewed by or released to auditors, CIHR or regulatory agencies. For participants who are invited to participate but refuse, the positive screen for the presence of OSA will be communicated to their treating physician as a "red flag" of potential significance for clinical care. The communication of such pertinent medical information was already included in the informed consent for the Brain Health Now study.

#### **Record Retention**

Data and study documents at all sites will be stored securely for 7 years, after which they will be destroyed in keeping with the privacy and confidentiality regulations and guidelines.

## Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study

### References

1. Cysique, L.A. and B.J. Brew, *Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression*. J Neurovirol, 2011. **17**(2): p. 176-83.
2. Heaton, R.K., et al., *HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study*. Neurology, 2010. **75**(23): p. 2087-96.
3. *American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual, n.e., Vol III. Westchester: American Academy of Sleep Medicine 2005*.
4. *National Collaborating Centre for Mental Health. The NICE guideline on the treatment of depression in adults*. Available from: <http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf>.
5. Gamaldo, C.E., et al., *Evaluating sleep and cognition in HIV*. J Acquir Immune Defic Syndr, 2013. **63**(5): p. 609-16.
6. Kilpinen, R., T. Saunamaki, and M. Jehkonen, *Information processing speed in obstructive sleep apnea syndrome: a review*. Acta Neurol Scand, 2014. **129**(4): p. 209-18.
7. Decary, A., I. Rouleau, and J. Montplaisir, *Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery*. Sleep, 2000. **23**(3): p. 369-81.
8. Beebe, D.W., et al., *The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data*. Sleep, 2003. **26**(3): p. 298-307.
9. Aloia, M.S., et al., *Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review*. J Int Neuropsychol Soc, 2004. **10**(5): p. 772-85.
10. Verstraeten, E., *Neurocognitive effects of obstructive sleep apnea syndrome*. Curr Neurol Neurosci Rep, 2007. **7**(2): p. 161-6.
11. Somers, V.K., et al., *Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health)*. Circulation, 2008. **118**(10): p. 1080-111.
12. Drager, L.F., J.C. Jun, and V.Y. Polotsky, *Metabolic consequences of intermittent hypoxia: relevance to obstructive sleep apnea*. Best Pract Res Clin Endocrinol Metab, 2010. **24**(5): p. 843-51.
13. Young, T., et al., *Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study*. Arch Intern Med, 2002. **162**(8): p. 893-900.

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

14. Tarasiuk, A. and H. Reuveni, *The economic impact of obstructive sleep apnea*. Curr Opin Pulm Med, 2013. **19**(6): p. 639-44.
15. Redline, S., et al., *Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment*. Am J Respir Crit Care Med, 2000. **161**(2 Pt 1): p. 369-74.
16. Peppard, P.E., et al., *Increased prevalence of sleep-disordered breathing in adults*. Am J Epidemiol, 2013. **177**(9): p. 1006-14.
17. Heinzer, R., et al., *Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study*. Lancet Respir Med, 2015. **3**(4): p. 310-8.
18. Gingo, M.R., et al., *Pulmonary symptoms and diagnoses are associated with HIV in the MACS and WIHS cohorts*. BMC Pulm Med, 2014. **14**: p. 75.
19. Triant, V.A., et al., *Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease*. J Clin Endocrinol Metab, 2007. **92**(7): p. 2506-12.
20. Kunisaki, K.M., et al., *Prevalence and correlates of obstructive sleep apnoea among patients with and without HIV infection*. HIV Med, 2015. **16**(2): p. 105-13.
21. McDaid, C., et al., *Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis*. Health Technol Assess, 2009. **13**(4): p. iii-iv, xi-xiv, 1-119, 143-274.
22. Bucks, R.S., M. Olaith, and P. Eastwood, *Neurocognitive function in obstructive sleep apnoea: a meta-review*. Respirology, 2013. **18**(1): p. 61-70.
23. Olaith, M. and R.S. Bucks, *Executive dysfunction in OSA before and after treatment: a meta-analysis*. Sleep, 2013. **36**(9): p. 1297-305.
24. Ancoli-Israel, S., et al., *Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study*. J Am Geriatr Soc, 2008. **56**(11): p. 2076-81.
25. Netzer, N.C., et al., *Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome*. Ann Intern Med, 1999. **131**(7): p. 485-91.
26. Ahmadi, N., et al., *The Berlin questionnaire for sleep apnea in a sleep clinic population: relationship to polysomnographic measurement of respiratory disturbance*. Sleep Breath, 2008. **12**(1): p. 39-45.
27. Chung, F., H.R. Abdullah, and P. Liao, *STOP-Bang Questionnaire: A Practical Approach to Screen for Obstructive Sleep Apnea*. Chest, 2016. **149**(3): p. 631-8.
28. Chung, F., et al., *Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients*. Anesthesiology, 2008. **108**(5): p. 822-30.
29. Mayo, N.E., M.J. Brouillette, and L.K. Fellows, *Understanding and optimizing brain health in HIV now: protocol for a longitudinal cohort study with multiple randomized controlled trials*. BMC Neurol, 2016. **16**: p. 8.
30. Brouillette, M.J., et al., *Quantifying cognition at the bedside: a novel approach combining cognitive symptoms and signs in HIV*. BMC Neurol, 2015. **15**(1): p. 224.

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

Appendix 1. Questionnaires screening for the presence of OSA administered as part of the main study

### **MERGED BERLIN AND STOP BANG QUESTIONNAIRE (FOR SLEEP APNEA)**

1. Do you snore?
  - a. Yes
  - b. No
2. If answer is yes, your snoring is:
  - a. Slightly louder than breathing
  - b. As loud as talking
  - c. Louder than talking
  - d. Very loud – loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night?
3. How often do you snore?
  - a. Nearly every day
  - b. 3-4 times a week
  - c. 1-2 times a week
  - d. 1-2 times a month
  - e. Never or nearly never
4. Has your snoring ever bothered other people?
  - a. Yes
  - b. No
  - c. Don't Know
5. Has anyone observed you Stop Breathing or Choking/Gasping during your sleep?
  - a. Yes
  - b. No

5.1 If people have noticed that you quit breathing during your sleep, how often does that happen?

  - a. Nearly every day
  - b. 3-4 times a week
  - c. 1-2 times a week
  - d. 1-2 times a month
  - e. Never or nearly never
6. How often do you feel tired or fatigued after your sleep?
  - a. Nearly every day
  - b. 3-4 times a week
  - c. 1-2 times a week
  - d. 1-2 times a month

**Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

- e. Never or nearly never

7. Do you often feel Tired, Fatigued, or Sleepy during the daytime?

- a. Yes
- b. No

7.1 If yes, how often do you feel Tired, Fatigued, or Sleepy during the daytime?

- a. Nearly every day
- b. 3-4 times a week
- c. 1-2 times a week
- d. 1-2 times a month
- e. Never or nearly never

8. Have you ever nodded off or fallen asleep while driving a vehicle?

- a. Yes
- b. No

**Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

Appendix 2: Standard protocol for initiation of CPAP in the home

See attached: Contact Management Schedule and Compliance with Telemonitoring

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

### Appendix 3: confirmation of collaboration

**From:** Perraud, Cecile [Cecile.Perraud@airliquide.com]

**Sent:** September 15, 2015 11:26 PM

**To:** Marta Kaminska, Dr; [marie-josee.brouillette@muhc.mcgill.ca](mailto:marie-josee.brouillette@muhc.mcgill.ca);  
[Cecilia.Costiniuk@muhc.mcgill.ca](mailto:Cecilia.Costiniuk@muhc.mcgill.ca)

**Cc:** Normandeau, Guy

**Subject:** RE: Etude VIH - apnee

Bonjour,

Avant tout, nous vous remercions de nous proposer de nous associer au projet.

Nous avons contacté les fournisseurs pour recevoir leur offre de fournitures.

Parallèlement et dans l'attente d'un courrier officiel que je vous soumettrai, vous pouvez d'ores et déjà compter sur le support de Vitalaire sur le volet initiation à la thérapie/formation/suivi.

Très sincèrement.

**Cécile Perraud**

Directrice Régionale

7100, rue Jean Talon Est - Bureau 100

H1M 3S3 MONTREAL-ANJOU, QC

Tel: (514) 728 2664 # 6021 - Mobile: (514) 378 7175

[cecile.perraud@airliquide.com](mailto:cecile.perraud@airliquide.com)

[www.VitalAire.com](http://www.VitalAire.com)



**From:** PERRAUD, Cecile [Cecile.Perraud@airliquide.com]

**Sent:** October 13, 2015 2:17 PM

**To:** Marta Kaminska, Dr; [marie-josee.brouillette@muhc.mcgill.ca](mailto:marie-josee.brouillette@muhc.mcgill.ca);  
[Cecilia.Costiniuk@muhc.mcgill.ca](mailto:Cecilia.Costiniuk@muhc.mcgill.ca)

**Cc:** NORMANDEAU, Guy

**Subject:** RE: Etude VIH - apnee

Bonjour,

Je vous reviens suite à nos rencontres avec les fournisseurs.

Le fournisseur Respiration serait intéressé mais doit soumettre le projet à un comité de sélection. Le processus de retour est de 12 semaines.

Le fournisseur Resmed est également intéressé et disponible pour approvisionner les équipements (masques et unités) selon notre demande. Si vous êtes d'accord, je vous propose d'aller de l'avant avec les produits Resmed, qui offrent toutes les fonctionnalités demandées pour votre projet. Nous pourrions organiser une démonstration de l'outil et ensuite bâtir le protocole de suivi avec vous.

Dans l'attente de votre retour,

Très sincèrement,

**Cécile Perraud**

Directrice Régionale

**From:** Marta Kaminska, Dr [<mailto:marta.kaminska@mcgill.ca>]

**Sent:** Tuesday, October 13, 2015 3:30 PM

16

## **Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

**To:** PERRAUD, Cecile; [marie-josee.brouillette@muhc.mcgill.ca](mailto:marie-josee.brouillette@muhc.mcgill.ca); [Cecilia.Costiniuk@muhc.mcgill.ca](mailto:Cecilia.Costiniuk@muhc.mcgill.ca)  
**Cc:** NORMANDEAU, Guy  
**Subject:** RE: Etude VIH - apnee

Merci pour le suivi.

Quand a moi je suis d'accord pour y aller avec Resmed.

Pour le protocol de suivi, il serait probablement concordant avec le protocol habituel clinique de VitalAire. Pourriez-vous nous en envoyer une copie? Nous pourrions ensuite voir s'il y a lieu d'y porter des modifications pour l'étude.

Salutations,

Marta Kaminska MD, M.Sc. FRCP(C)  
McGill University Health Centre  
Respiratory Division / Sleep laboratory  
1001 Decarie Blvd, Montreal, Qc, Canada  
H4A 3J1  
tel: 514-934-1934 ext 35650/36117  
fax: 514-843-1695  
[marta.kaminska@mcgill.ca](mailto:marta.kaminska@mcgill.ca)

**"NORMANDEAU, Guy"**  
**<Guy.Normandea@airliquide.com>**  
04/12/2016 05:11 PM

To "marie-josee.brouillette@muhc.mcgill.ca" <marie-josee.brouillette@muhc.mcgill.ca>  
cc  
Sub Rabais CPAP - Projet VIH  
ject

Après avoir revérifier toutes nos ententes je suis heureux de t'informer que les patients que nous accueillerons dans le cadre du projet de recherche sur le VIH pourront jouir d'un rabais de 20% sur l'appareil CPAP au moment de l'achat.

Excuse ma lenteur dans ce dossier.

Cordialement,

**Guy Normandea**  
Chef de secteur/Area Manager – Quebec

**Effect of Continuous Positive Airway Pressure (CPAP) treatment on cognitive ability in HIV+ individuals with obstructive sleep apnea (OSA): A pilot study**

Appendix 4: VitalAire consent to collect and communicate information  
See attached