Obstructive Sleep Apnea Endotypes and Impact on Phenotypes of People Living With HIV

Research Plan

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

Obstructive Sleep Apnea Endotypes and Impact on Phenotypes of People Living with HIV

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

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4. ESTIMATED DURATION OF THE STUDY

4 years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Obstructive sleep apnea (OSA) is a very common disease, which might explain some of the symptoms experienced by people living with human immunodeficiency virus (HIV), such as fatigue and heart disease. We seek to understand how the different underlying causes of OSA affect the way people living with HIV (PLWH) experience OSA. We also want to understand how symptoms of obstructive sleep apnea improve with treatment, and if this too, is affected by the underlying cause of OSA in that individual

6. SPECIFIC AIMS

Aim 1*:* To compare the symptoms of PLWH+OSA vs. PLWH–OSA. This aim will allow us to test the hypothesis that fatigue is overexpressed in PLWH+OSA compared to PLWH-OSA, independent of known covariates. We will develop a multivariate model to predict fatigue based on clinical accessible data.

Aim 2: In those PLWH found to have OSA, we will:

a. Compare neurocognitive performance [psychomotor vigilance test (primary outcome), NIH Toolbox Cognition] in PLWH+OSA with low arousal threshold vs. those with a high arousal threshold. We hypothesize that stratified for similar disease severity, low arousal threshold induced OSA yields worse neurocognitive dysfunction compared to equal severity OSA with high arousal threshold.

b. Compare endothelial function (arterial tonometry) in PLWH+OSA with high loop gain (ventilatory instability with associated hypoxemia/hypercapnia) vs. those with low LG, to test the hypothesis that stratified for similar disease severity, LG-induced OSA yields worse endothelial function compared to equal severity OSA with low LG.

Aim 3: To test in PLWH+OSA whether 3 months of PAP treatment results in changes in OSA manifestations. This aim will allow us to test the hypothesis that endotype underlying OSA will be predictive of the specific clinical improvements seen in adherent users of PAP therapy. For example, those with high LG at baseline will have the greatest improvement in endothelial dysfunction with PAP therapy compared to other OSA patients with similar disease severity as measured by AHI.

7. BACKGROUND AND SIGNIFICANCE

People Living with HIV: The availability of effective and generally well-tolerated antiretroviral therapy for people with HIV has translated into dramatically longer survival and life expectancy. It is estimated that more than 50% of those with HIV infection in the US are now >50 years old.[1] While efforts at disease prevention and cure are needed and ongoing, an important focus is now on understanding the symptoms and co-morbidities of people living with HIV. For example, fatigue is very commonly reported by PLWH even while HIV is suppressed and with normal CD4 counts.[2,3] Nearly half of HIV-infected adults report poor sleep quality.[4] Coronary artery disease and diabetes mellitus are now recognized as important complications of ART.[5,6] One relatively unexplored co-morbidity that may link these symptoms and complications in PLWH is obstructive

sleep apnea (OSA).

Sleep in HIV: Sleep problems have long been recognized as a prominent symptom in HIV.[54,55] Given the high prevalence of sleep problems across multiple cohorts, sleep was included in the HIV symptom index, developed in 2001.[56] Again, fatigue remains a common symptom even in the modern era.[5,6] While fatigue and sleepiness are two very different constructs and can be attributed to different medical conditions, we note that patients often use these terms interchangeably and both are prominent and common symptoms of OSA (and HIV).[57]

Obstructive Sleep Apnea: OSA is defined by repetitive collapse of the upper airway during sleep, which leads to transient hypoxemia and arousals from sleep. Surges in sympathetic activity and sleep fragmentation lead to cardiovascular (e.g. hypertension, stroke, myocardial infarction) and neurocognitive (e.g. excessive daytime sleepiness, poor work performance, auto accidents) consequences. Recent estimates suggest that roughly 10% of the US population has clinically important OSA (roughly 13% of men and 6% of US women), the high prevalence reflecting aging of the population and the obesity pandemic, both factors known to contribute to OSA risk.[7,8] The most commonly prescribed treatment for OSA is continuous positive airway pressure (CPAP), which acts as a pneumatic stent to keep the upper airway open during sleep. CPAP is effective, but poorly tolerated and adherence is low.[9]

OSA is a multifactorial disease with different manifestations – Endotypes and Phenotypes: OSA is increasingly recognized as a multifactorial disorder i.e., different people have OSA for different reasons. Although an anatomical predisposition (collapsibility of the upper airway) is generally required, other factors are important as well, including a low respiratory arousal threshold (wake up too easily), dysfunction in upper airway dilator muscles and instability in ventilatory control (which we quantify using the engineering term loop gain [LG]) which leads to periods of decreased pharyngeal tone.40 The ultimate goal of our work is to personalize therapy for OSA one day by addressing the underlying endotype to treat OSA effectively in an individual with targeted therapy.41

Different patients with OSA may also have different symptoms, and variable risk of certain co-morbidities. That is, two patients of the same gender, weight and OSA severity, as defined by the apnea-hypopnea index (AHI), may have very different observable consequences of OSA, or phenotypes. The concept of OSA phenotypes has been advanced by multiple groups. For example, Ye and colleagues found 3 distinct clusters of OSA types based on sleep questionnaire responses, which they labelled the “disturbed sleep”, “minimally symptomatic”, and “excessive daytime sleepiness” groups.42 The clusters did not differ based on sex, BMI, or sleep apnea severity. However, the clusters did vary in associations with hypertension and cardiovascular disease, a finding consistent with other studies.43,44 Although AHI is frequently used to assess OSA severity, AHI does not correlate strongly with most relevant OSA co-morbidities.45,46 A related observation is that while treatment of CPAP can improve blood pressure, the effect is highly variable across individuals.47 Taken together, these observations suggest that the expression of OSA in an individual is often variable.

One example that illustrates these concepts is OSA endotypes and phenotypes in the elderly. OSA is very common in the elderly, and treatment is likely to be important. However, the symptoms of OSA experienced by younger and older adults are often different.48 For example, Kobayashi and colleagues showed that although OSA severity as assessed by AHI or oxygen desaturation was similar between younger and older OSA, those diagnosed only later in life were less sleepy objectively or subjectively compared to those who were diagnosed at a younger age. Also, epidemiological data have clearly shown that OSA cardiovascular complications in the elderly are less than in younger people for the same degree of OSA severity.49 Thus, the presenting symptoms, and rationale for treatment may be different in younger vs. older patients with OSA.

OSA in PLWH: A recent study by Patil and colleagues found that a major proportion of HIV-infected subjects

(70% of the studied cohort) had OSA.[10] Given the greatly improved long-term survival now common among PLWH, aging and obesity are increasingly prevalent in PLWH, which might explain this finding. However, the PLWH were younger and substantially leaner (as assessed by BMI) than the controls in this study – and therefore would have been expected to have a lower prevalence of disease. Furthermore, current or prior ART use was associated with an increased prevalence of OSA (90 vs 57%), again, even though the prior ART group had a lower BMI. Thus, there appears to be an unexpectedly high prevalence of OSA in PLWH not predicted by traditional risk factors. The lack of traditional risk factors may explain very low rates of OSA diagnosis (<4%) in some cohorts.[11,12]

Untreated OSA is also likely to be relevant for symptoms in PLWH. Witnessed apnea, a fairly specific marker of OSA, was a predictor for clinically relevant fatigue in PLWH.64 Not only do PLWH complain of fatigue, they also complain with equal frequency of daytime sleepiness (defined as Epworth Sleepiness Score >11). Although these may be distinct symptoms with distinct underlying causes, the two terms are often closely intertwined and/or used interchangeably by patients. Untreated OSA is likely to be important for ongoing inflammation. The presence of moderate or severe OSA was associated with an increased odds (OR 6.9) of C-reactive protein > 3.0mg/dL.65 In those with untreated disease it was also associated with viral load >10,000 copies/mL (OR 7.1), as well as a higher TNF-alpha level.

Unfortunately, few PLWH and OSA are treated. Perhaps because PLWH with OSA are younger and thinner than those without HIV and OSA, or because common OSA symptoms like fatigue/tiredness are ascribed to HIV, few PLWH have been diagnosed with OSA. In multiple practice settings [the Veterans Aging Cohort Study (VACS), in an urban clinic, and in an academic University CFAR clinic1] only about 4% of PLWH were diagnosed with OSA. Although OSA is often under-diagnosed in general, in the same Veterans Cohort the rate of OSA diagnosis in non HIV was 12.4%. Thus, few patients or providers consider OSA in PLWH, although it is highly likely to be important for many comorbidities.

Thus, our overall hypotheses are 1) that OSA is incredibly common and underdiagnosed in PLWH, 2) that OSA has consequences for PLWH, and 3) that underlying endotype of OSA influences disease expression and response to treatment.

8. PROGRESS REPORT

N/A (initial submission)

9. RESEARCH DESIGN AND METHODS

Under each visit subsection, we have added alternatives for researchers to consider in order to maintain social distancing and perform study activities remotely due to COVID-19. After written informed consent has been obtained, the following procedures will be undertaken:

Daytime Visit 1 (Aim #1)

1. *Anthropomorphic assessment:* Baseline demographics and health status (medical problems, medications, allergies, social history) will be obtained. A basic exam, including height, weight, neck circumference, hip, and waist circumference, blood pressure, and oxygen saturation will be obtained.
2. *Lung Function Assessment using spirometry*: As per American Thoracic Society criteria. In brief, subjects will blow into a pneumotachogram via a mouthpiece with a nose clip in place from full inhalation to complete exhalation.

3. *Questionnaires:* Standard sleep related questionnaires will be used, including the Epworth Sleepiness Scale, Pittsburg Sleep Quality Index, and Insomnia Severity Index (ISI). In addition subjective assessment of fatigue, depression, quality of life questionnaires, pain, and alcohol consumption will be

used including Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), Beck Depression Index-II, SF-36 Item Health Survey (SF-36), Brief Pain Inventory (Short Form), PROMIS pain intensity, PROMIS pain interference, Alcohol Use Disorders Identification Test (AUDIT), and Alcohol Dependence Scale (ADS). Subjects will also be given the FRAM body morphology questionnaire.

4. *Neurocognitive assessment*: Subjective assessment will be done using, Patient's Assessment of Own Function Inventory (PAOF) questionnaire. Objective assessment of brain function will be done using 10 minute psychomotor vigilance test (PVT). Neurocognitive assessment will be done using NIH Toolbox Cognition. This battery yields three composite scores: overall cognitive function, crystallized cognition and fluid cognition. The two tests of "crystallized cognition" are less sensitive to acquired brain dysfunction and reflect past learning experiences (Oral Reading Recognition and Picture Vocabulary). The five tests of "fluid cognition" assess multiple cognitive domains that are vulnerable to acquired brain dysfunction (i.e., Picture Sequence Memory Task = episodic memory, Dimensional Change Card Sort Task = executive function/flexibility, Pattern Comparison Task = processing speed, Flanker Inhibitory Control and Attention Task = executive function/inhibitory control, and List Sorting Task = working memory).

The NIH Toolbox battery has been nationally normed in a sample of 4,859 participants, English or Spanish speaking, ages 3-85 years, representative of the U.S. population based on gender, race/ethnicity, and socioeconomic status. Based on these data, demographically-corrected T-scores are available to adjust for age, gender, education, language and race/ethnicity.115 Additionally, this assessment tool is the result of an NIH initiative and is used in many studies, which allows for harmonization of findings. It can be completed in approximately 30 minutes.

5. *Cardiovascular assessment:* Standard blood pressure and peripheral artery tonometry (PAT). Endothelial vasodilator function will be assessed using the EndoPAT 2000 (Itamar Medical, Caesarea, Israel) device. The EndoPAT test has been shown to be highly predictive of traditional cardiovascular risk factors. This test takes approximately 15 minutes. EndoPAT measures digital pulse amplitude with the probes placed on the tip of each index finger. The EndoPAT probe comprises a pneumatic plethysmograph that applies uniform pressure to the surface of the distal finger, allowing measurement of pulse volume changes in the finger. Digital pulse amplitude will be measured during three stages from both right and left index fingers. Arterial flow of one arm will be occluded for 5 minutes by a blood pressure cuff placed on a proximal forearm at a pressure of 60 mm Hg above the systolic blood pressure or 300 mm Hg (whichever is higher). The digital pulse amplitude of the non-occluded arm will be measured as the control baseline. The three stages of the test will be: 1) Before occlusion (resting period) - digital pulse amplitude will be recorded for 5 min at rest; 2) During arterial flow occlusion- arterial flow occlusion will be applied in one arm and digital pulse amplitude will be recorded for another 5 min; 3) After occlusion- the cuff is rapidly deflated to reverse the occlusion and digital pulse amplitude recorded for 5 minutes to assess peripheral vasodilator response to reactive hyperemia.

If time/equipment does not allow for performance of these procedures, subjects will be asked to complete it just prior to their sleep study, or during an additional visit (for which they would receive additional compensation).

6. *Actigraphy*: Subjects will be fitted with a **wristworn actigraph to measure activity and light exposure** which they will wear for 2 weeks after their overnight study to estimate rest/activity cycle. We will use the Actiwatch Spectrum Pro (Philips Respironics) which is the size of a wrist watch and weighs just 31 grams. We recognize that forced dyssynchrony and constant routine are the gold standards for assessment of endogenous

circadian rhythm, and we are supportive of such efforts in PLWH. Nevertheless, for the purposes of this application we believe we can use actigraphy coupled with examination by a Sleep Medicine expert to diagnose clinically relevant circadian disorders (such as advanced sleep phase disorder). The information from actigraphy will also be relevant in assessing activity levels and sleep/rest duration.

We anticipate that all of these procedures will take up to 4 hours. Per ACTRI clinic requirements, all subjects that are anticipated to remain at our study location over 2 hours will have to complete a COVID-19 swab. Our research group and/or the university will cover all charges associated with COVID-19 testing. Only subjects that are negative for SARS-CoV-2 virus can participate in the 4-hour visit.

Shortened in person Daytime Visit + Remote Daytime Visit #1

If COVID-19 is still a concern, we will split the daytime visit, so that it consists of a shortened in person daytime visit and remote daytime visit.

We will obtain consent during the in person daytime visit and complete the following study activities--anthropomorphic assessment, lung function test, EndoPat, and neurocognitive assessment (NIH toolbox). An actigraphy watch will be given during the shortened daytime visit or mailed to the subject's home.

For the remote daytime visit, participants will be sent a personalized RedCap link in order to complete general health and sleep questionnaires. A researcher will be present on the phone to help troubleshoot and guide the remote daytime visit. The PI will also reach out to the subject to complete a structured interview over the phone or via Zoom in order to get a list of previous and current medications and substances they have used.
Overnight Visit #1. Due to the COVID-19 pandemic, the ACTRI clinic is requiring that subjects complete a COVID-19 swab within 72 hours of their overnight appointment. Only subjects that are negative for COVID-19 are allowed to complete this visit. Please note these requirements are subject to change. Subjects will arrive to the research sleep laboratory at approximately 8PM and undergo the following procedures:

1. Polysomnography: Monitoring for standard clinical polysomnography study will be applied to the subject, as follows: The subject will have EEG, EMG, EOG, and ECG electrodes, an adhesive body position sensor placed in standard locations. Pulse oximetry sensor will be attached either to a finger or ear lobe and secured by tape. The following parameters will be measured during sleep: electroencephalogram, eye movement, electrocardiogram, electromyogram, leg movement, snoring sounds, nasal pressure, and nasal-oral airflow by thermistor, respiratory effort and body position by piezo-electric bands of the thorax and abdomen or magnetometers, position sensors, and pulse oximetry. This equipment is standard for diagnostic polysomnography and should not be uncomfortable.

Once all of this equipment has been comfortably and securely fastened, the subject will be allowed to fall asleep and data recording will begin. Subjects will be asked to remain in the supine position as much as possible. All data will be acquired on a 1401 plus interface and Spike 2 software. The study will end at approximately 6 AM, at which time the monitoring equipment will be removed, and the subject will undergo a blood draw in this fasting state.

If eligible participants are unable to come in for the overnight sleep research study, a Home Sleep Test with EEG instrumentation with be performed.

Home Sleep Test: A sleep technician will arrive at the subject's home to apply the following:
Chest belt is secured around the chest to detect respiratory motion. Respiration is further monitored by placing a nasal flow cannula in the nostrils to detect nasal airflow. A pulse oximeter probe will be clipped to the finger

or earlobe for continuous oxygen saturation monitoring. Apneas and hypopneas will be defined using the recently published American Academy of Sleep Medicine (AASM) guidelines for syndrome definition and scoring techniques. We will provide the HST report to these subjects. If they are eligible to participate in our study based on the HST result, we will explain the study and protocols and informed consent to participate in specific arms of the study will be reviewed with the subjects in details.

The study will end at approximately 6AM. The equipment will be removed and given to the sleep technician.

2. *Phlebotomy*: Venipuncture will be performed by a certified research staff or physician using standard techniques and appropriate blood borne pathogen precautions. Approximately 10-15 cc of blood will be drawn in the morning at wake into serum separator and EDTA tubes. Serum samples will be immediately processed to separate serum, which will be stored in darkness at -70 F to preserve until analysis can be conducted. EDTA tubes will be processed and refrigerated for use within 24 hours. Blood will also be collected to measure high sensitivity C Reactive Protein (hsCRP), insulin, glucose (to calculate HOMA-IR), cytokines such as IL-6 and TNF-alpha.[119] We will also store plasma for other potential markers, to explore other interactions, such as markers of liver disease like ALT and AST. Fluids collected may be stored indefinitely and/or used in additional research to be conducted by study investigators associated with the HIV Neurobehavioral Research Program (HNRP) conducting IRB approved research. Samples and data collected in the course of the study will be banked and may be sent to other research scientists anonymously (without identification).

Generally, blood samples will be collected in the morning after the first polysomnography visit is completed. On occasion, subjects will be asked to come in on a separate day to complete their fasting morning blood draw, if staff or blood processing team are not available. Subjects will be scheduled to complete this blood draw during a 15 minute appointment between 7AM-8:30AM. Since this is a fasting blood draw, subjects will come in fasting (without food) and will be permitted to have water only.
Subjects will then be able to go home. They will leave the actiwatch for the investigators. We anticipate that Overnight Visit #1 will last 10 hours (most of which will be spent asleep).

Remote Overnight Visit #1

If COVID-19 is still a concern, subjects will be given a Home Sleep Test (HST) to complete after their first daytime visit. Instructions of how to use the HST can be offered through a secure Zoom video call and written instructions. Participants will be given the option to pick up the HST from the ACTRI clinic or to have it mailed to their address. A research technician will be on-call for questions and troubleshooting the night the subject completes their overnight sleep study.

Subjects will have to be scheduled for a separate morning visit to have their blood drawn.

If subjects are not found to have OSA, they will not continue with the study.
(End of Aim #1)

Aims #2 and #3
Subjects found to have OSA (with AHI >5 events/hour) will be referred for clinical evaluation (by a sleep physician not involved in the study) and treatment, and will also return for overnight visit #2, and continue to be followed with weekly phone calls and a repeat assessment 3 months after starting OSA treatment.

<u>Overnight Visit #2</u> (Aim #2) Measurement of Endotypic Traits

This visit will be scheduled to occur within 1 month of visit 1, and will be prior to any clinical OSA treatment. Subjects will come to the sleep research laboratory about 2-3 hours before their usual bedtime. They will undergo polysomnography, as described above, without the physiological CPAP testing procedure. To review, the subject will have EEG, EMG, EOG, and ECG electrodes, an adhesive body position sensor placed in standard locations. Pulse oximetry sensor will be attached either to a finger or ear lobe and secured by tape. The following parameters will be measured during sleep: electroencephalogram, eye movement, electrocardiogram, electromyogram, leg movement, snoring sounds, nasal pressure, and nasal-oral air flow by thermistor, respiratory effort and body position by piezo-electric bands of the thorax and abdomen or magnetometers, position sensors, and pulse oximetry. This equipment is standard for diagnostic polysomnography and should not be uncomfortable.

Additional equipment for the physiological sleep study will also be applied to the subject, as follows:

A thin esophageal catheter (6-8 french) with an electrode array to measure diaphragm electromyography will be placed via the nares. Prior to the cannula placement the subject will received 2 sprays of a nasal decongestant (0.05% oxymetazolime hydrochloride), followed by 4% lidocaine topical spray for local anesthesia. The catheter will be confirmed to be in the proper position by examining the signal, then taped to the nose (and later secured to the CPAP mask). The esophageal catheter placement may be omitted by subject or investigator request; in this case subjects can still remain in the study.

A standard CPAP mask will be placed over the nose and secured with velco straps. If necessary, the subject's mouth will be either taped closed or a chin strap applied to ensure nasal breathing. A specially modified continuous positive airway pressure (CPAP) device (ResMed, San Diego, CA) that delivers both positive and negative airway pressure will be connected to the mask. Once all of this equipment has been comfortably and securely fastened, the subject will be allowed to fall asleep and data recording will begin. Subjects will be asked to remain in the supine position as much as possible. All data will be acquired on a 1401 plus interface and Spike 2 software (Cambridge Electronics Design Ltd, Cambridge, UK).

After sleep onset, airway pressure will be increased in order to abolish flow limitation. During sleep, a previously validated sequence of pressure reductions will be performed in order to measure respiratory control and upper airway characteristics, as follows: The holding pressure will be abruptly changed to atmospheric pressure for several breaths, then returned to holding pressure. After a short time, the pressure will be gradually reduced over the course of several minutes, until an arousal occurs on the EEG (generally not associated with any awareness by the subject). The subject will be given several minutes to resume normal sleep, and the procedure will be repeated until three stable readings are obtained. Subsequently, the procedure will be repeated, but with a reduction in pressure to a level that does not induce arousal. After a short period of time with stable breathing at this pressure, the pressure will be returned to the holding pressure to measure ventilatory response. This will be repeated until 3 stable values are obtained.

The study will end at approximately 4 AM, at which time the monitoring equipment will be removed, and the subject will be allowed to go home. However, if the subject is still sleepy, they will be allowed to sleep with CPAP applied until they feel rested.
Aim #3 investigates the impact of CPAP on the phenotypic traits.

We anticipate that Overnight Visit #2 will last 8 hours (most of which will be spent sleeping).

Supplemental Daytime Visit (optional)
Subjects will be asked to complete this visit, if 12 weeks have lapsed between the first visit and the start of their PAP therapy. Subjects will repeat all of the same measurements described under Visit 1.

APAP Device Given to Subjects (optional)
Subjects will be offered a trial of a clinical Automatic Positive Airway Pressure (APAP) for up to 3 months, while they are waiting for their clinical evaluation from a sleep physician. Dr. Owens will oversee management of the device. APAP is a smart positive airway pressure (PAP) device, where the pressure changes as needed to provide optimal pressure to splint the upper airway.

Supplies will be given for the purposes of the study and returned after 3 months, during the final daytime visit. If the subject is unable to complete the study, the device will be returned during an appointment to pick up study compensation. If the APAP unit is no longer functioning when it is returned, the subject will not be charged for the damages. Additionally, if the device becomes unusable before the subject finishes the trial, we will ask that the device be returned in exchange for a functional APAP device. Alternatively, if the subject is unable to come to our study location, we will send out the replacement device and provide postage for the broken device.

Weekly Phone calls: Subjects will be referred to a sleep physician for PAP therapy. The treatment is expected every day to be worn when participants are asleep (including naps). In addition to usual clinical care provided to ensure optimal adherence to PAP therapy, the research staff will be in weekly contact with subjects to provide encouragement, and identify and troubleshoot impediments to all-night, every-night use of PAP therapy. These phone calls will be 10-15 minutes each for 12 weeks.

2 weeks prior to returning for Daytime Visit #2, subjects will be mailed or delivered an actiwatch to wear for 2 weeks.

Daytime Visit #2: Impact of OSA treatment on Sleep and Activity Phenotypes

> After three months of OSA treatment, subjects will return to the sleep lab to repeat all of the same measurements described under Visit 1 with the exception of the lung function testing (see Daytime Visit #1). This visit will generally occur in the morning at which time another fasting blood sample will be collected. If the fasting blood sample cannot be collected during this visit, a separate visit will be scheduled. Subjects will be scheduled to complete this blood draw during a 15 minute appointment between 7AM-8:30AM. Since this is a fasting blood draw, subjects will come in fasting (without food) and will be permitted to have water only.

Additionally for subjects uing PAP therapy for treatment of OSA, we will obtain a PAP download which will report therapeutic holding pressure, residual apnea-hypopnea index, as well as multiple parameters of adherence such as days of use, number of days >4 hours per night, etc. Mask type (nasal vs. oronasal, etc) will be recorded. The actiwatch will be returned to the investigators to assess the impact of PAP therapy on activity levels, pattern of activity and sleep duration.

We anticipate that Daytime Visit #2 will be 2 hours.

Shortened Daytime Visit and Remote Daytime Visit #2

As an alternative to having subjects come in for their final visit, subjects can complete the following activities remotely:

Subjects will be asked to complete all the questionnaires via a RedCap link. A researcher will remain on the phone in order to guide subjects and troubleshoot issues. The remaining study activities (anthropomorphic

assessment, lung function test, EndoPat, neurocognitive assessment) (NIH toolbox), 10 minute PVT, and blood sample) will have to be completed during a separate shorter daytime visit. An actigraphy watch may be mailed to the subject's home in order for data to be collected before their final daytime visit.

The total duration of the participant's involvement in the study is expected to be a total of 18 weeks.

Summary Information:

Clinical and research procedures: All of the study procedures are intended for research purposes only. However, it is anticipated that we will discover some previously undiagnosed sleep disorders, mostly obstructive sleep apnea. These subjects will be referred for a clinical sleep evaluation and treatment. rocedures carried out solely for research purposes: Overnight sleep studies (polysomnogram), pulmonary function testing, arterial tonometry (endoPAT), venipuncture, exhaled nitric oxide and carbon monoxide measurements

Devices: This study does not use any devices considered experimental or investigational. The sleep study equipment is FDA exempted. All FDA-regulated devices used in this study are approved for the proposed subject population and purpose. No significant risk devices are in use during this study.

Research material: Physiological recordings will be obtained as stated above. Records will be created within the native format of the software associated with the equipment, using the subject identifier (no protected health information). Similarly, blood samples will be labeled with subject identifiers. The study will maintain a database for future research purposes; however, any future projects will undergo a separate IRB approval prior to using this data/material.

Data collection and analysis: Raw data will be collected in the native format of each device, with use of subject ID rather than any PHI. For example, sleep studies will be collected in Spike2. Signal analysis will be performed in MATLab. The master database for the study will be maintained within UCSD's RedCap system behind a protected firewall. Data will be analyzed using statistical software such as SPSS or R.

Women and Minorities: Women and minorities will be included in this study in a fashion that is non-biased from the screened population.

Correspondence Letters to Our Research Subjects
After a subject has completed the Overnight Study #1, a letter offering their preliminary result will be given or mailed to them. Subjects who have completed the study will also be sent a letter thanking them for their participation and explaining that study results should be published in a manuscript after data analysis is complete.

10. HUMAN SUBJECTS

People living with HIV (n=120) will be recruited into the study to undergo a standard sleep study (polysomnogram, PSG), a research sleep study, and PAP trial.

Inclusion Criteria:
- Ages 18-65years old
- BMI 20 – 35 kg/m^2
- Physician diagnosis of HIV and viral suppression

Exclusion Criteria:
- Pregnancy

- Inability to complete study procedures, such as questionnaires that are only available/validated in English.
- Already on effective therapy and adherent to treatment for OSA
- Other known untreated sleep fragmenting disorder, such as periodic limb movement disorder, or narcolepsy

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Subjects will be recruited from the following sources: 1) IRB- approved flyers or advertisements, with prospective subjects initiating contact with the research staff, 2) Persons who have participated in prior research studies from our laboratory or affiliated laboratories who have indicated that they would like to be contacted to hear about potential research studies, 3) Patients from the UCSD Pulmonary and Sleep Center, UCSD Owen Clinic, and VA SPID clinic who have indicated that they are interested in hearing about research opportunities, and 4) Persons who have been identified via SlicerDicer

Identifying Eligible Subjects with Partial HIPAA Waiver

A temporary waiver of consent and partial waiver of HIPAA authorization is requested for this study in order to: 1) Pre-screen persons (from sources 2 and 3 above) who meet the inclusion and exclusion criteria, and 2) Perform telephone or in person interviews with potential subjects for screening of inclusion and exclusion criteria prior to obtaining consent. The following points justify the waiver of consent: 1) Private information that will be reviewed is non-sensitive, and anyone pre-screened will have previously agreed to contact for research, 2) No research procedures will be performed without consent, so there should be minimal possibility of adverse effect on potential subjects, 3) Adequate enrollment could not be achieved without accessing this information, since specific medical conditions are being investigated, 4) All persons contacted will be provided with information about our screening procedures. For the partial HIPAA authorization: 1) Any PHI accessed for screening will be kept by research staff until either consent is obtained, or it will be destroyed immediately if consent and HIPAA authorization is not obtained, 2) Identifying potential subjects and then contacting/approaching them to discuss the research will require accessing PHI, 3) Minimal necessary PHI will be accessed and kept only temporarily while that subject is being screened, as above, 4) PHI will only be accessed by members of the research team included in the IRB, and will include name, date of birth, medical record number, contact information, and diagnoses.

SlicerDicer

Slicer Dicer will be used to identify both Summary & Patient Level Requests:
Researchers plan to use UC San Diego Health's Epic SlicerDicer, a self-service cohort discovery tool. Researchers will have access to direct summary and patient level data. Using SlicerDicer, researchers will: Review the charts at a patient level to identify potential patients for recruitment.
We will be identifying patients with Human Immunodeficiency Virus (HIV), ages 18-65 years, and without other known untreated sleep fragmenting disorder. We will create a call list with the patient's name, phone number, and email address. This call list will be stored digitally under password protection on a UCSD secured drive shared between the research team. Once identified, an investigator of the study team will contact the patient to ask if are interested in hearing about sleep medicine research study opportunities. If yes, the study team member will provide full details about the study. If no, the patient's name will be removed from the call list. All Epic Slicer Dicer users will have access and security provided by UCSD's Epic access team.

Prospective subjects will also be recruited from the community after individuals have initiated contact with the research staff. Permission to distribute IRB approved messages and flyers is being requested for the following

sites and locations.

UCSD Listserve, UCSD Hospital Bulletin Board, Facebook, Craigslist, UCSD CTRI REDCap Survey
IRB approved flyers will be digitally posted on the UCSD Listserv, Facebook, and Craigslist. The flyers will also be placed on UCSD Hospital Bulletin Boards by the Community Engagement Manager for the Clinical Transitional Research Institute (CTRI).

Facebook Page Welcome Message
We are requesting permission to have this message posted on a Facebook page created for recruitment purposes.

> Welcome to the UCSD Pulmonary and Sleep Medicine Research group's Facebook page. We have ongoing research studies, primarily investigating obstructive sleep apnea. If you or someone you know has obstructive sleep apnea, please see our IRB approved flyers below. Occasionally, we are looking for healthy individuals without sleep disorders. Please regularly check our page for flyers describing these research opportunities.

Research Match
ResearchMatch will be used to contact prospective subjects with an IRB approved recruitment message. The message will be submitted for approval in an amendment if it is not already included with the initial project submission.

Department of Motor Vehicles Booth
The Research Team will set up a booth between the hours of 8AM-5PM outside of the Clairemont Department of Motor Vehicles (DMV) at 4375 Derrick Drive, San Diego, CA 92117 to distribute IRB approved flyers. A permit application for Activity on State Property will be submitted to the California Highway Patrol for approval at least 30 days before the booth is prepared.

Radio Station (list of radio stations)
We are requesting permission to have the following message broadcasted on iHeartMedia San Diego radio stations--Star 94.1, 101.5 KGB, Channel 93.3, Rock 105.3, XTRA 1360 Fox Sports, KOGO: 600 AM, JAM'N 95.7--KPBS 89.5 FM, Jazz 88.3 FM, KFSD 1450 AM, KURS 1040 AM, and AM 1170 The Answer:

> UCSD Pulmonary and Sleep Medicine Research is offering research study opportunities, primarily for people with sleep apnea. If you or someone you know suffers from obstructive sleep apnea, contact us at (858) 246-2154 or sleepresearch@ucsd.edu for more information.

When this message is IRB approved, it will be submitted only to the radio stations listed above. We will request permission for any additional radio broadcasting stations.

Research Group Website
The UCSD Pulmonary and Sleep Medicine Research group has a webpage hosted by UCSD health sciences. Wording from IRB approved flyers will be posted there.

UCSD CTRI REDCap Survey
Prospective subjects can voluntarily choose to fill out a UCSD CTRI REDCap Survey for this protocol. Information will be securely collected and stored via REDCap and will be used to determine if the prospective subject is eligible for the study.

MyChart Messages

UCSD Owen clinic patients may be sent a letter via MyChart by their clinicians inviting them to participate in this research study. Please see the document entitled "MyChart Letter for Owen Clinic patients" for the message.

12. INFORMED CONSENT

The research coordinator will screen the subjects over the telephone (or in person for clinic patients, time and patient preference allowing) following the screening script. A waiver of documented consent will be requested and once oral consent by the subject is obtained this consent will be used for the sole purpose of discussing the study with the subjects over the phone and performing the screening process as needed. The reason for this is because the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Individuals interested in participating in this study will be given detailed explanation of the procedures, potential benefits, risks and discomforts of the study by the study researchers listed in the IRB application. All study staff are CITI certified and the importance of following GCP and HIPAA rules has been impressed upon them by the PI. Staff obtaining consent will have sufficient knowledge of the study to answer any questions that might arise during the consent process.

A copy of the consent form will be given to the potential subject by email a minimum of 48 hours in advance of any planned baseline visit. If the individual agrees to participate, they will meet with research staff in person prior to any data collection to obtain written informed consent. Subjects who have given a written consent will be given a copy of the signed consent form. The original consent and HIPAA authorization will be kept in the subject's research file in a locked cabinet. No research procedures will be performed prior to obtaining informed consent.

English will be used in all discussions during the consent process. The patient will be excluded from the study if their preferred language is one other than English or if they do not understand English. The information being communicated will not include any exculpatory language through which the potential subject will waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the University or its agents from liability for negligence. Subjects unable to give their own consent will not be included in the study.

As this study is separate from any clinical care, a waiver of the requirement to upload the consent and HIPAA waiver into the electronic medical record is requested.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to study participation is not to participate. Subject may choose not to participate in this research study if they wish.

14. POTENTIAL RISKS

Sleep Studies: During the sleep portion of the study, there may be discomfort at the electrodes sites; a localized skin irritation/allergy can occur due to application of the skin surface electrodes for EEG, EKG, and EMG recordings. Subjects may be sleepy after participating in our physiology studies if they have poor sleep.

During the physiological sleep studies, the tight-fitting nasal mask could lead to skin irritation, nasal congestion, and/or nasal dryness. Short periods of apnea during the study would not be expected to cause side effects, other than the possibility of awakening from sleep. Finally, when using positive pressure or having one's mouth taped closed, there is a rare risk of vomiting, which could in turn lead to aspiration, but this is

exceedingly rare and minimal overall risk.

For esophageal catheter placement, there is mild discomfort associated with passing the catheter through the nose and potential gagging or even vomiting as the catheter passes through the pharynx. However, once in place the catheter is not uncomfortable and is well tolerated. All subjects will have fasted for at least four hours prior to the study and thus their stomach content is minimal. The mask can be easily removed if needed for any reason. For these reasons we believe there is a minimal risk of aspiration or other complication from this portion of the study.

Venipuncture: Local bruising and soreness can occur, which are usually mild and self limited.

EndoPAT: Tingling of the hands following cuff inflation can cause discomfort but goes away within a few minutes. No permanent injury has been reported by the manufacturer.

Lung function testing: The test is routinely performed in clinical practice with few associated risks. Lightheadedness or coughing may be induced by forceful breathing.

Loss of Confidentiality: There is a risk of loss of subject confidentiality. We will protect all subject information to the best of our ability so this will not happen, as detailed in subsequent sections.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

We believe the risks of our research are quite minimal. All recordings will be performed in the closely monitored environment of our research laboratory in the CTF, CTRI, or MTF. Emergency equipment and personnel are readily available in the unlikely event of a serious complication.

Following the overnight study, subjects will have the option of sleeping, without instrumentation, for as long as they would like before driving home. We will offer them a cab voucher to have a cab take them home. They will only drive home if they feel adequately rested to do so and is corroborated by an assessment by a health professional (MD, PhD, or equivalent) trained in sleep medicine. The subject will be assessed for excessive sleepiness. If subject does not feel comfortable driving home, we will offer them a cab or they will be allowed to continue sleeping.

Subjects will be given a phone number to report any post-study complications, which will be personally reviewed by the PI to determine whether they require additional follow up or warrant reporting to the IRB as a serious unanticipated event. Because this is a research study, there may be some unknown risks that are currently unforeseeable. Any abnormal findings discovered as part of the study, will be relayed to the subject and, if requested, to their PCP. For example, persistently high blood pressure measurements or high fasting glucose will be communicated to the subjects and to their doctor.

DSM Report

A data safety monitoring report will be prepared at least annually and included with reports to the UCSD HRPP (yearly continuing review) and the funding agency (yearly progress report). In addition to enrollment, it will track:

1) All adverse events in which abnormal testing results were conveyed to the subject.
2) All adverse events in which abnormal testing results were conveyed to a subject's designated physician. (A record of this communication will be kept in the patient's file.)
3) Any other adverse events, serious adverse events, and unanticipated problems, all of which will be adjudicated and classified as study-related or unrelated to the study.
4) The report will also include amendments to the study protocol.

This yearly report will be comprehensive; however, more prompt reporting may be needed.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

There is always the risk of subject information being released accidentally. We will make every effort to maintain patient privacy and confidentiality both during and following the study. Electronic study data will be de-identified by substitution of codes for names and hospital identifiers and will be stored on a secure disk for access by Investigator and study staff only and any hard copies will be stored in a locked cabinet.In all correspondence and in internal study reports that require identification of individual subjects, subjects will be referred to and known by their ID number and character name code. HNRP staff will have access to data collected from research subjects that have previously participated in protocol with their research division. All subject data forms (CRF's) will only list the ID number. All research staff are CITI certified and have had impressed upon them the importance of confidentiality. This study does not involve the collection of sensitive personal information from subjects. Data will be stored only at UCSD sites and its use will be confined to that specified in this protocol and its approved amendments.

Data generated as a result of this study will only be made available for inspection upon request of the UCSD Human Research Protection Program or the study sponsor.

17. POTENTIAL BENEFITS

Subjects who participate may derive benefit if a previously unknown sleep disorder such as obstructive sleep apnea is diagnosed and treated. Subjects who are not found to have OSA or other sleep disorder are unlikely to derive benefit. Society in general may benefit as this study will help achieve a more complete understanding of breathing disorders.

18. RISK/BENEFIT RATIO

The investigators feel risks associated with these studies are outweighed by the benefits.

19. EXPENSE TO PARTICIPANT

There will be no cost to the subject for participating in this study. All of the tests and procedures that will be done for this research will be paid for by study funds. We will pay for any sleep studies done for research purposes.

Subjects diagnosed with sleep apnea who are recommended to undergo treatment for OSA and elect to do so may have expenses incurred. For example, they may have a co-pay as part of their clinical sleep evaluation, or as part of their OSA treatment.

20. COMPENSATION FOR PARTICIPATION

Subjects will be compensated after completing each portion of the study, as outlined below:

- Daytime Visit 1 (Aim 1): $50
- Overnight Visit 1 (Aim 1): Routine Polysomnography:$100
- Actiwatch returned (Aim 1): $50Overnight Visit 2 (Aim 2): Research Polysomnogram: $100
- Weekly Phone calls (Aim 3): Subject will be compensated for $20 for answering each weekly follow-up call for 12 weeks, in total of $240.
- Daytime Visit 2 (Aim 3): Day Testing $50
- Actiwatch Returned (Aim #3): $50
- If a separate visit needs to be scheduled for the fasting morning blood sample: $20 for each visit
- If an additional daytime visit is needed for data collection: $50
- If data is inconclusive and an additional polysomnogram night is required, they will be paid $100.

Subjects will make up to a total of $-660.00 for completion of the all study aims, unless additional data needs to be collected.

If subjects only complete Aim 1, compensation will be $200.00.

If subjects only complete Aim 1 and Aim 2, compensation will be $300.00.

Parking will be available free of charge and participants will also be reimbursed for minor out of pocket expenses including meal vouchers, public transportation or taxi vouchers. If the subject terminates the study early, they will receive an amount based on the visits that have been completed. If any of the visits are missed, the subject will not be compensated for those visits.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

All physicians performing physical exams (PEs) and taking medical histories are medically licensed in the State of California. The personnel performing the sleep and physiology studies are experienced medical researchers and certified sleep technologists.

- Robert Owens, MD, is a physician in the Division of Pulmonary, Critical Care, and Sleep Medicine and has privileges at the UCSD Health System. As the Principle Investigator, Dr. Owens will oversee the study, responsible for recruitment, consenting and answering questions with the study subjects, data analysis, and interpretation of study results. He has experience in all aspects of the proposed research.

- Atul Malhotra, MD, is chief of the Division of Pulmonary, Critical Care, and Sleep Medicine, and has privileges at UCSD Health System. Dr. Malhotra has very extensive clinical research experience in sleep disorders and is considered a world expert in sleep apnea physiology. As Co-I, he will be responsible for consenting subjects, assisting with research procedures, data analysis, interpretation of study results, and final report writing processes.

- Maile Young Karris, MD, is a physician in the Division of Infectious Diseases and has privileges at the UCSD Health System. As Co-I, she will be assisting with subject recruitment, answering subjects' questions, data analysis, interpretation of study results, and final report writing processes.

- Jeremy Orr, MD, is a physician in the Division of Pulmonary, Critical Care, and Sleep Medicine and has medical privileges through UCSD Health System. As Co-I, he will be responsible for consenting subjects, assisting with research procedures, data analysis, interpretation of study results, and final report writing processes.

- Christopher Schmickl, MD, is a physician in the Division of Pulmonary, Critical Care, and Sleep Medicine and has medical privileges through UCSD Health System. As Co-I, he will be responsible for consenting subjects, assisting with research procedures, data analysis, interpretation of study results, and final report writing processes.

- Omar Mesarwi, MD, is a physician in the Division of Pulmonary, Critical Care, and Sleep Medicine and has medical privileges through UCSD Health System. Dr. Mesarwi will act as the designated medical monitor, who will help adjudicate any potential adverse event.

- Naomi Deacon, PhD, is a postdoctoral researcher who will As Co-I, She will be responsible for consenting subjects, assisting with research procedures, data analysis, interpretation of study results, and final report writing processes.

- Pamela DeYoung is a board Registered Polysomnography Technologists (RPSGT) and will be responsible for recruitment, consenting subjects, running overnight sleep studies, and scoring of the data. Pam will also serve as the IRB Contact for this protocol.

- Naa-Oye Bosompra, Stacie Moore, Rebbecca Brena, Dillon Gilbertson and Janelle Fine are research assistants for Dr. Owens who will be responsible for recruitment, consenting subjects, running overnight sleep studies, and scoring of the data. Naa-Oye will serve as the IRB Administrative Contact for this protocol.

- Matthew Dawson is a research associate for the project who supervises and trains the psychometrists performing neuropsychological testing. He also oversees quality assurance of neuropsychological data and assists in performing analyses and writing manuscripts.

- Donald Franklin is a research associate who will act as liaison between the HNRP and Dr. Owens's staff at to ensure successful collaboration. He will also perform analyses and write manuscripts as needed.

- Everardo Aguilar is a bi-lingual Community Health Program Representative who has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; he has been authorized by the Principal Investigator to serve in this role.

- Robert Bryan is a Community Health Program Representative who has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; he has been authorized by the Principal Investigator to serve in this role.

- Susanna Concha-Garcia is a bi-lingual Senior Community Health Program Representative who has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; she has been authorized by the Principal Investigator to serve in this role.

- Roberto Gallardo is a bi-lingual Community Health Program Representative who has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; he has been authorized by the Principal Investigator to serve in this role.

- Allison Py is a community outreach worker who screens and schedules eligible participants for the study. She has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; she has been authorized by the Principal Investigator to serve in this role.

- Manuel Romero is a bi-lingual Community Health Program Representative who has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; he has been authorized by the Principal Investigator to serve in this role.

- Daisy Soria is a bi-lingual community outreach worker who screens and schedules eligible participants

for the study. She has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; She has been authorized by the Principal Investigator to serve in this role.

- Crossby Vargas is a bi-lingual Community Health Program Representative who has completed certification in the Protection of Human Research Subjects and has received specialized training to conduct and document the informed consent process for this study; he has been authorized by the Principal Investigator to serve in this role.

- Shannon Wright will serve as the Fiscal Contact for this protocol.

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23. FUNDING SUPPORT FOR THIS STUDY

Funding from NIH under 1R01HL142114-01

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable

26. IMPACT ON STAFF

This study is outside of any clinical care and thus will not impact any staff outside the research personnel. It is anticipated that we will diagnose 60 subjects with sleep disorders that require clinical evaluation over 4 years. This volume of patients can easily be handled by the UCSD Sleep Medicine clinic.

27. CONFLICT OF INTEREST

The PI and any key personnel associated with this study do not have any financial interests or other conflicts related to this study.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

This study will include enrollment of cancer patients. PRMC has determined that this protocol is not cancer-related.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable